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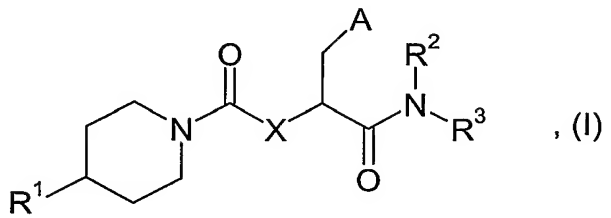
Veröffentlicht:
— *mit internationalem Recherchenbericht*
— *vor Ablauf der für Änderungen der Ansprüche geltenden Frist; Veröffentlichung wird wiederholt, falls Änderungen eintreffen*

[Fortsetzung auf der nächsten Seite]

(54) Title: SELECTED CGRP-ANTAGONISTS, THEIR PREPARATION PROCESSES AND THEIR USE AS MEDICAMENTS

(54) Bezeichnung: AUSGEWÄHLTE CGRP-ANTAGONISTEN, VERFAHREN ZU DEREN HERSTELLUNG SOWIE DEREN VERWENDUNG ALS ARZNEIMITTEL



, (I)

(57) Abstract: CGRP-antagonists are disclosed having the general formula (I), in which A, X and R^1-R^3 have the definition given in claim 1, as well as their tautomers, diastereomers, enantiomers, hydrates, mixtures and salts, as well as their salt hydrates, in particular their physiologically compatible salts with inorganic or organic acids, medicaments containing these compounds, their use and their preparation processes.

(57) Zusammenfassung: Gegenstand der vorliegenden Erfindung sind die CGRP-Antagonisten der allgemeinen Formel (I) in der A, X und R^1 bis R^3 wie in Anspruch 1 definiert sind, deren Tautomere, deren Diastereomere, deren Enantiomere, deren Hydrate, deren Gemische und deren Salze sowie die Hydrate der Salze, insbesondere deren physiologisch verträgliche Salze mit anorganischen oder organischen Säuren, diese Verbindungen enthaltende Arzneimittel, deren Verwendung und Verfahren zu ihrer Herstellung.

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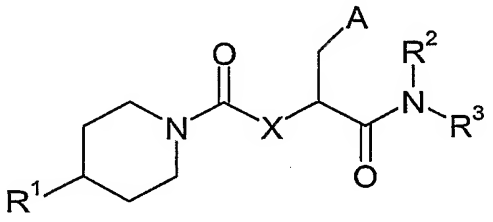
Zur Erklärung der Zweibuchstaben-Codes und der anderen Abkürzungen wird auf die Erklärungen ("Guidance Notes on Codes and Abbreviations") am Anfang jeder regulären Ausgabe der PCT-Gazette verwiesen.

Ausgewählte CGRP-Antagonisten, Verfahren zu deren Herstellung sowie deren Verwendung als Arzneimittel

Gegenstand der vorliegenden Erfindung sind die CGRP-Antagonisten der allgemeinen Formel

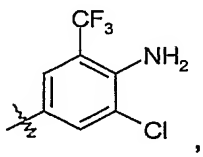


, (I)

deren Tautomere, deren Diastereomere, deren Enantiomere, deren Hydrate, deren Gemische und deren Salze sowie die Hydrate der Salze, insbesondere deren physiologisch verträgliche Salze mit anorganischen oder organischen Säuren, diese Verbindungen enthaltende Arzneimittel, deren Verwendung und Verfahren zu ihrer Herstellung.

In der obigen allgemeinen Formel (I) bedeuten

A einen Rest der Formel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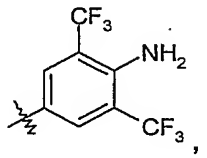
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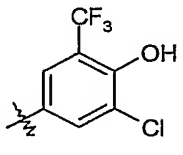
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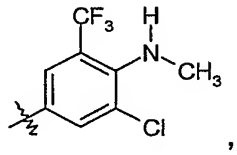
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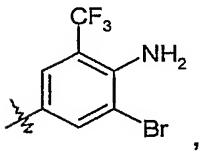
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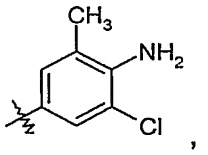
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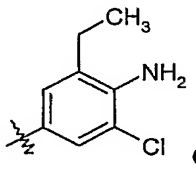
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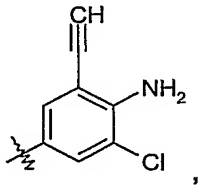
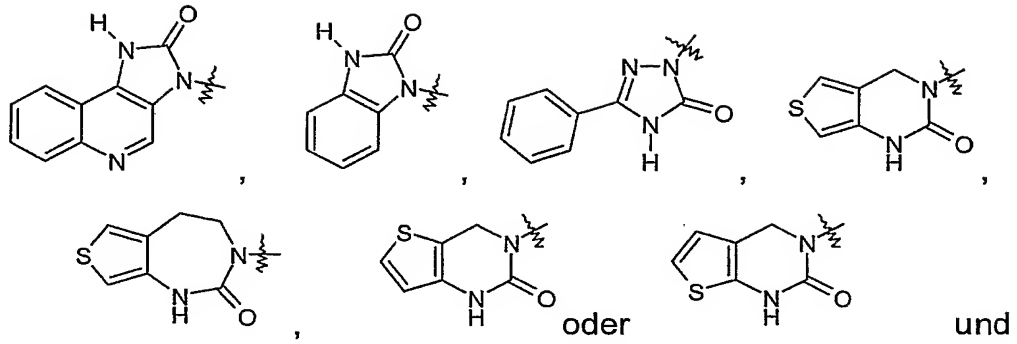
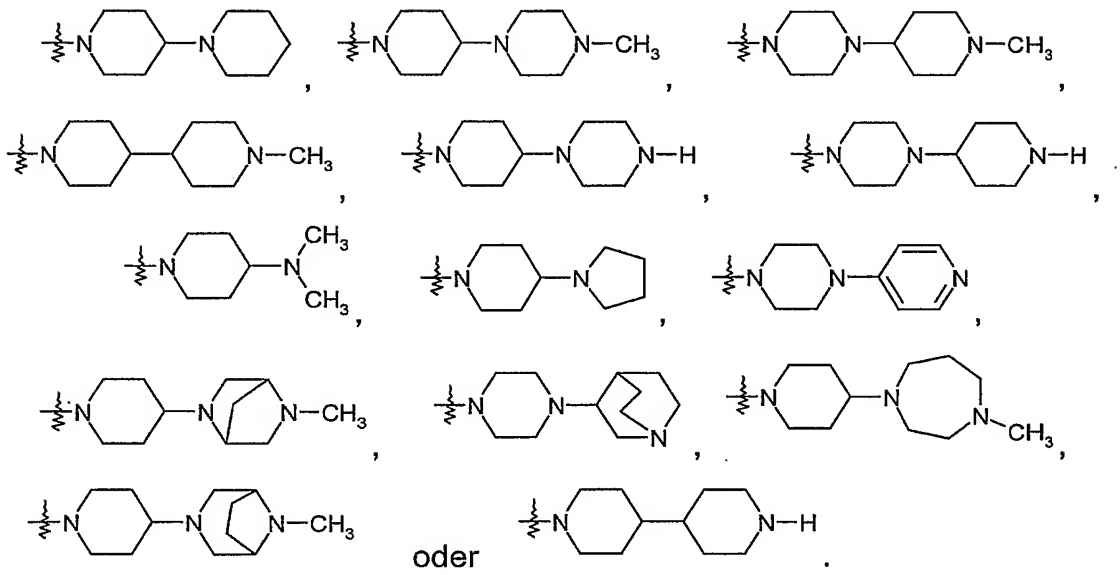

,

X ein Sauerstoffatom, eine Methylen- oder NH-Gruppe,

R^1 einen Rest der Formel


oder und

-NR^2R^3 einen Rest der Formel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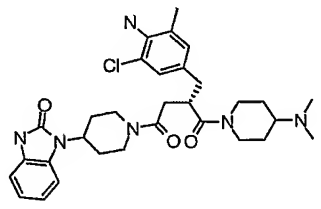
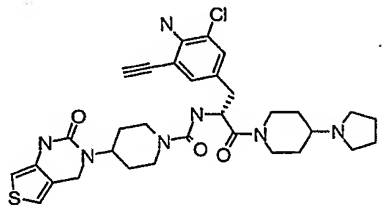
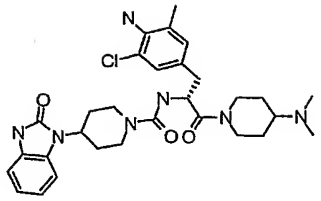
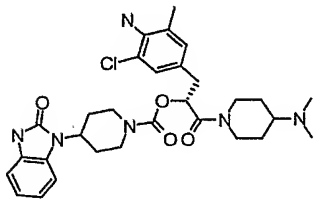
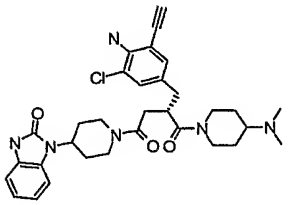
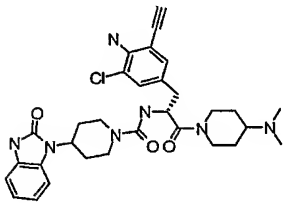
1 

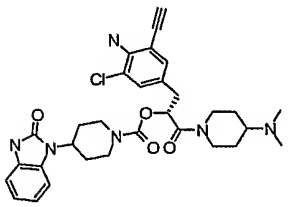
151 

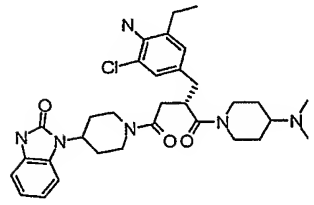
2 

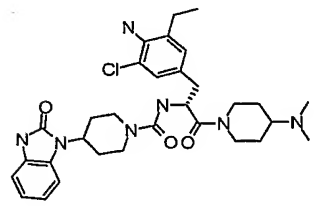
3 

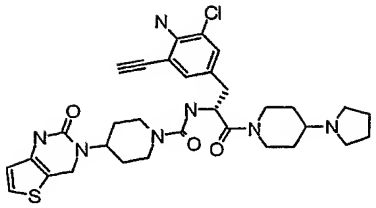
4 

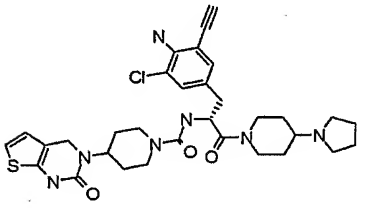
5 

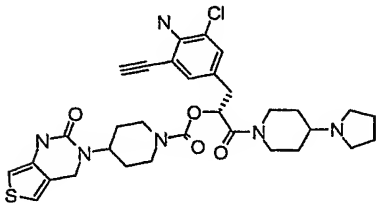
6 

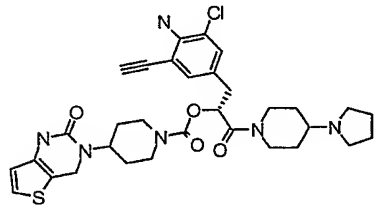
7 

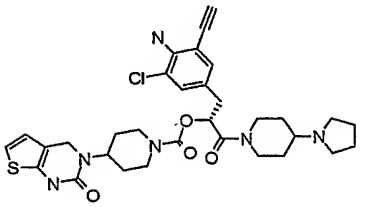
8 

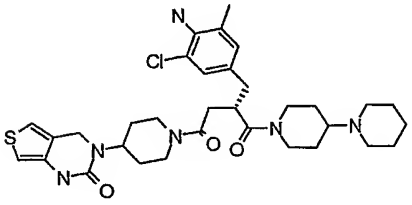
152 

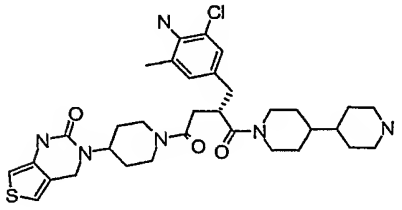
153 

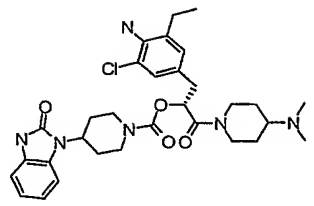
154 

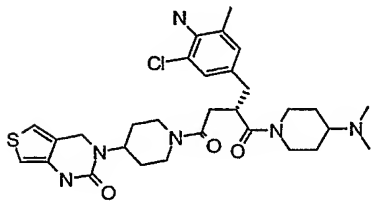
155 

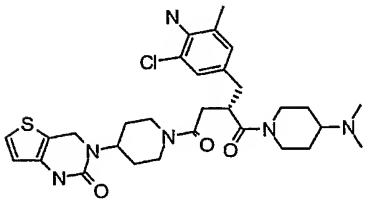
156 

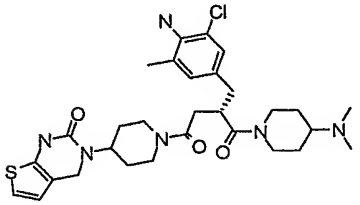
157 

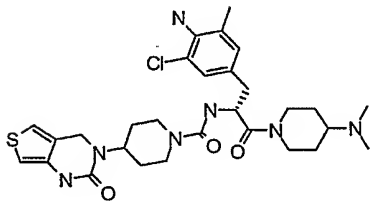
158 

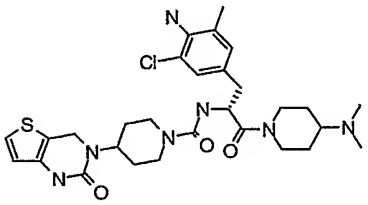
9 

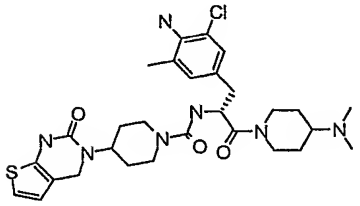
10 

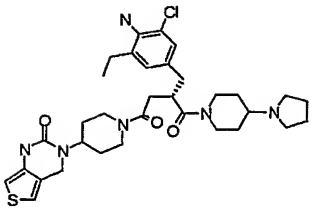
11 

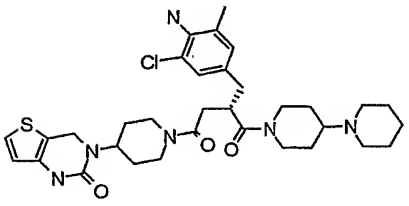
12 

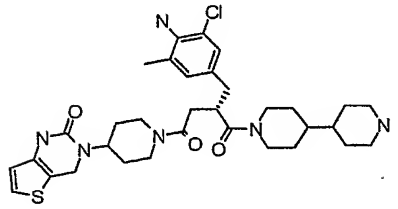
13 

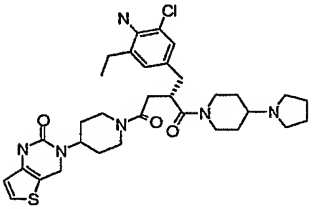
14 

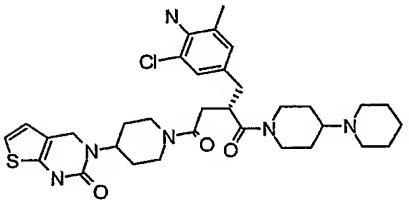
15 

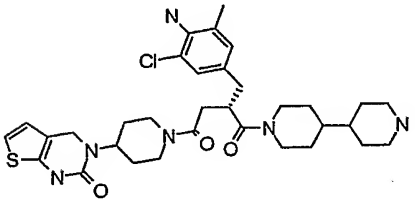
159 

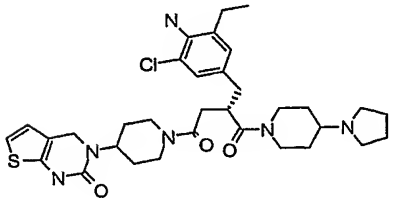
160 

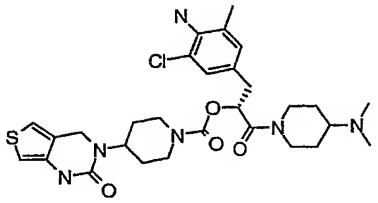
161 

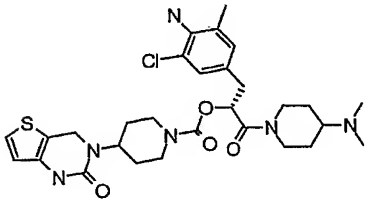
162 

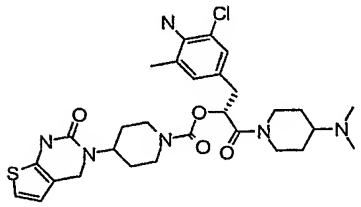
163 

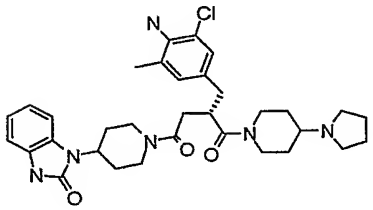
164 

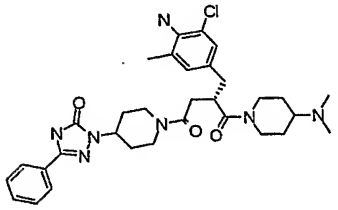
165 

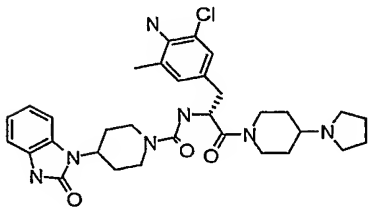
16 

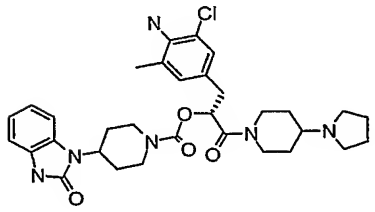
17 

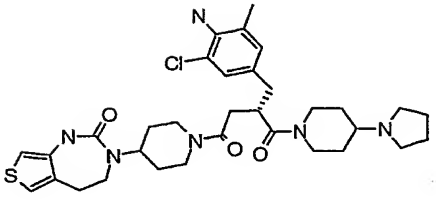
18 

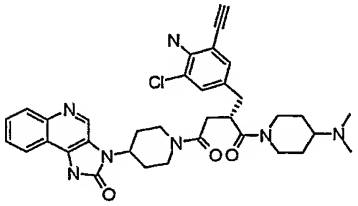
19 

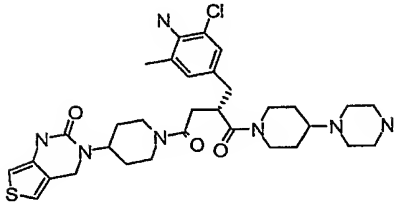
20 

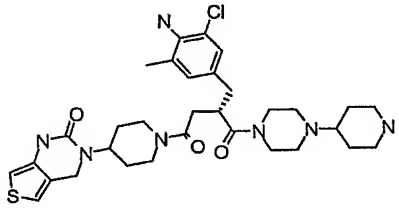
21 

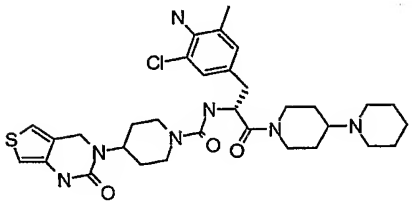
22 

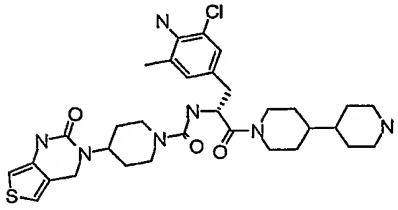
166 

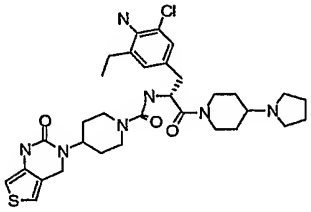
167 

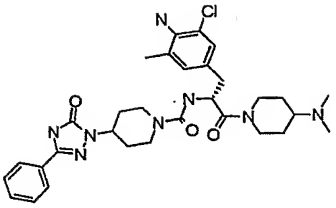
168 

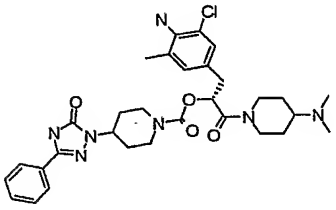
169 

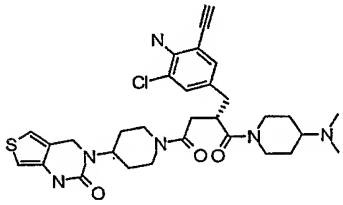
170 

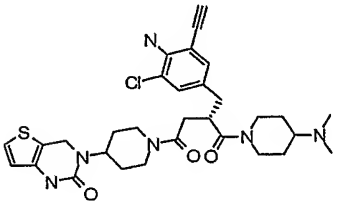
171 

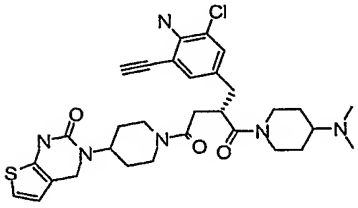
172 

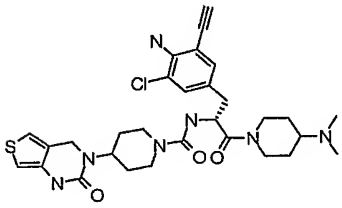
23 

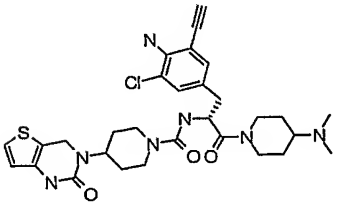
24 

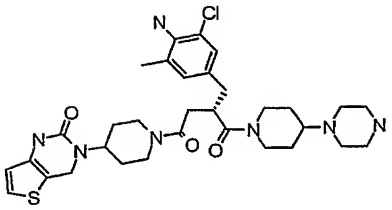
25 

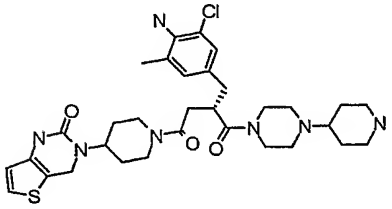
26 

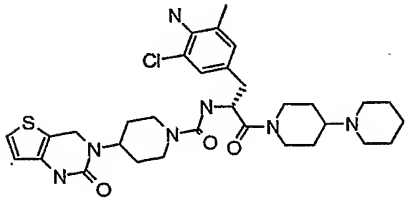
27 

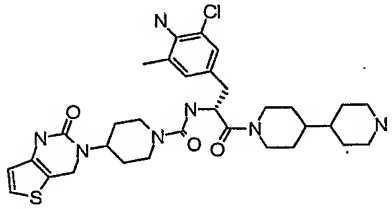
28 

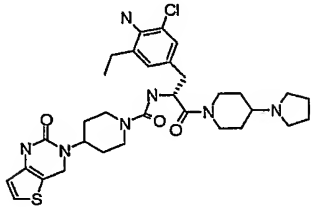
29 

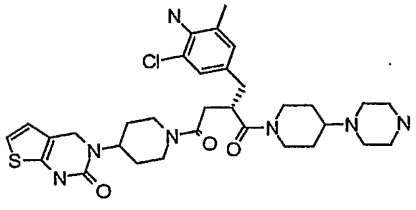
173 

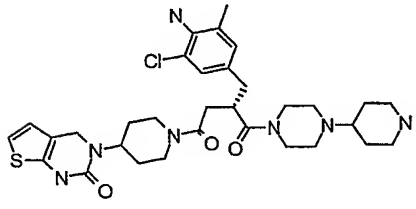
174 

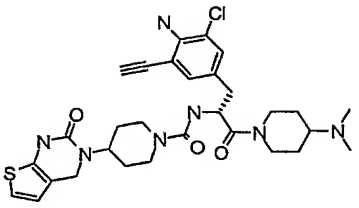
175 

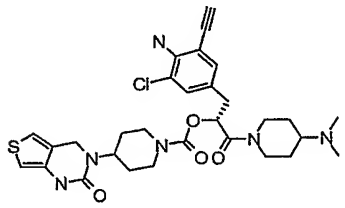
176 

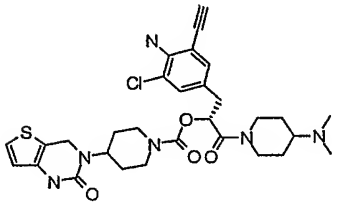
177 

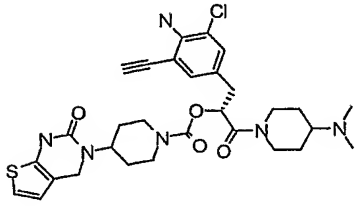
178 

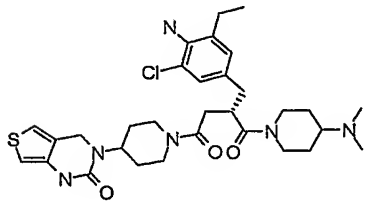
179 

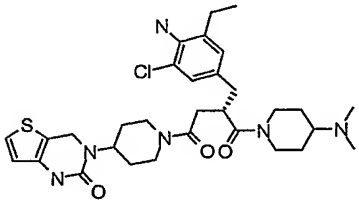
30 

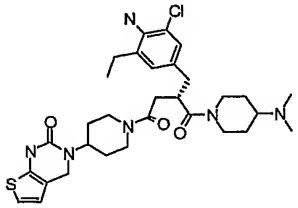
31 

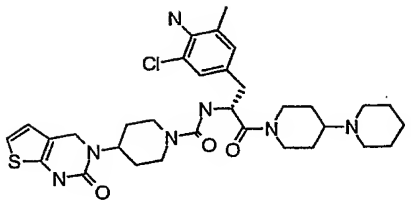
32 

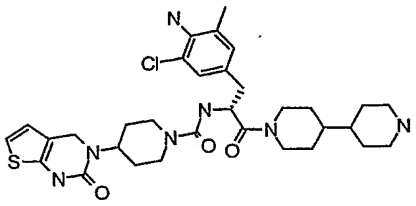
33 

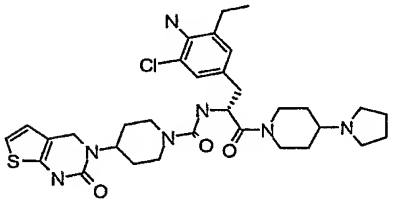
34 

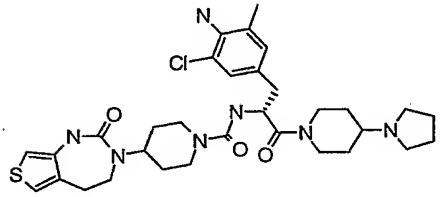
35 

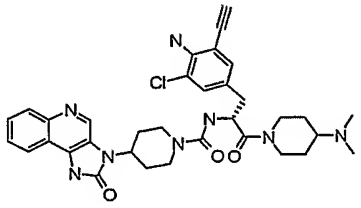
36 

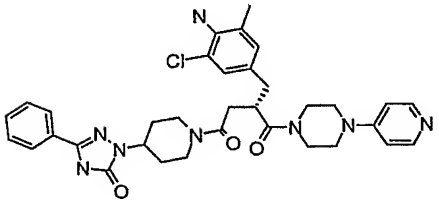
180 

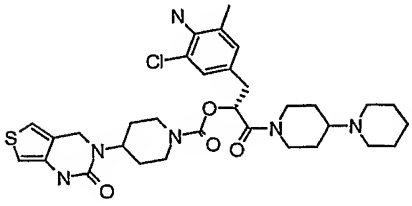
181 

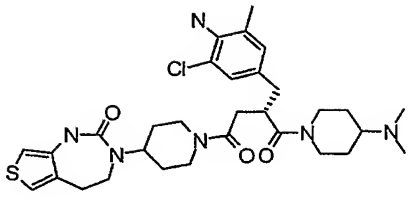
182 

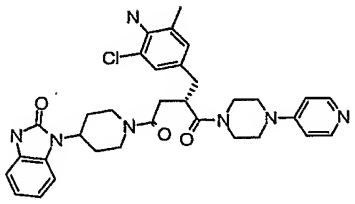
183 

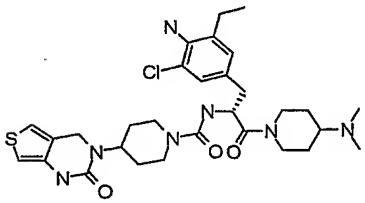
184 

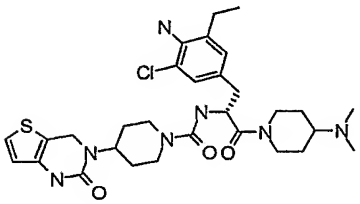
185 

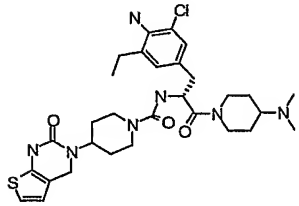
186 

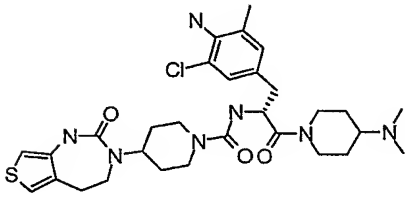
37 

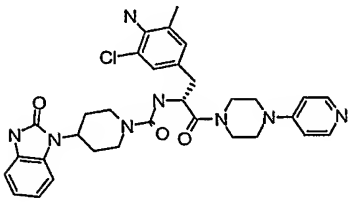
38 

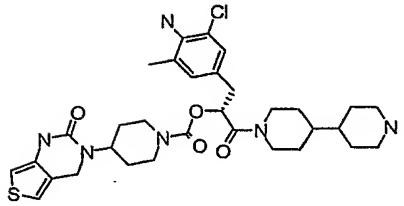
39 

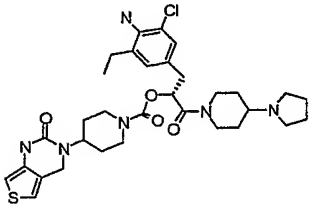
40 

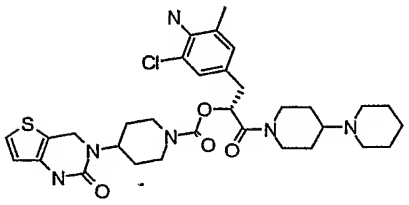
41 

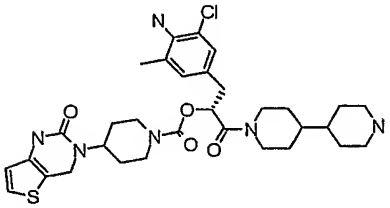
42 

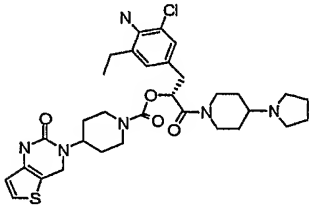
43 

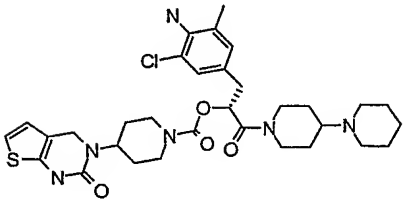
187 

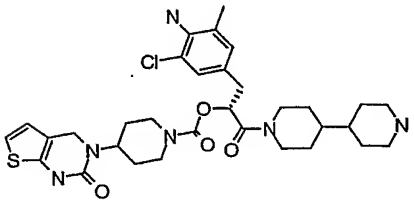
188 

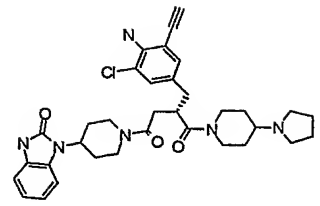
189 

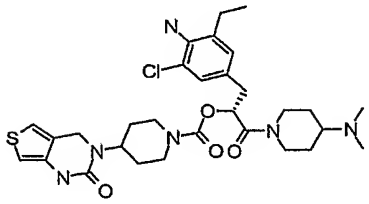
190 

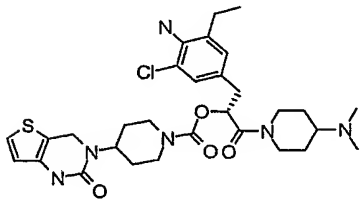
191 

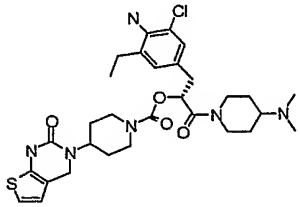
192 

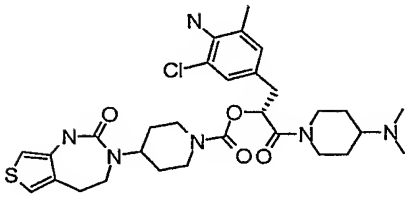
193 

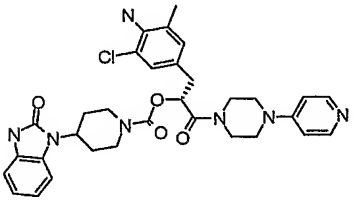
44 

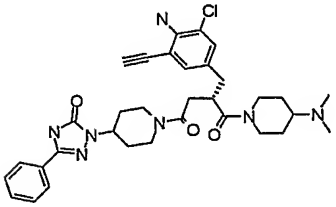
45 

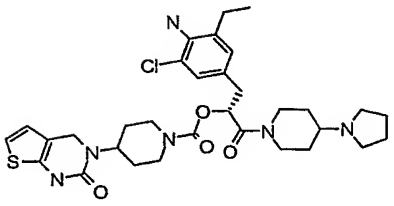
46 

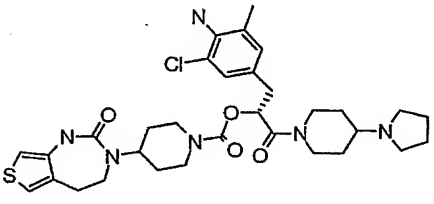
47 

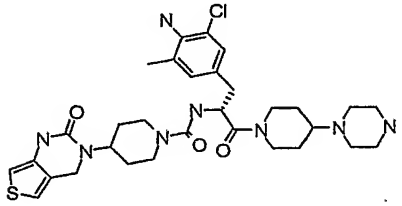
48 

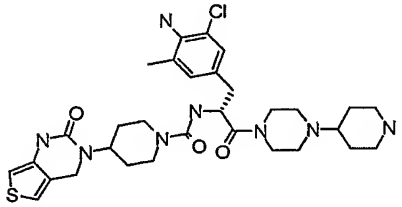
49 

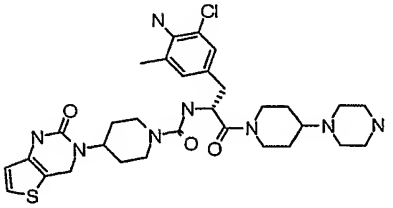
50 

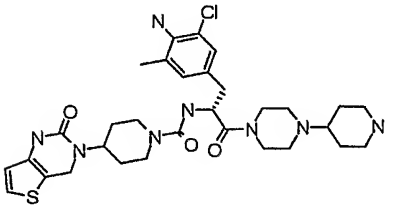
194 

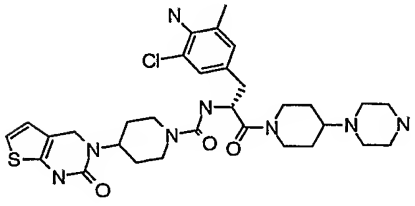
195 

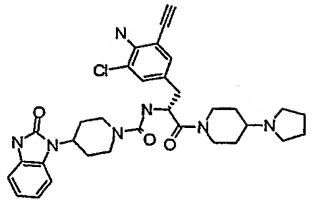
196 

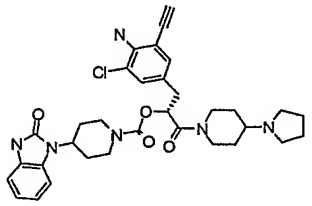
197 

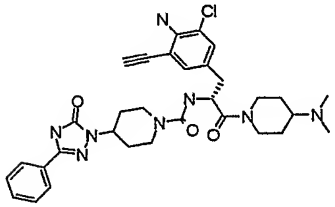
198 

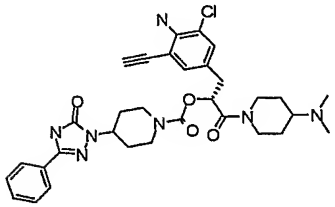
199 

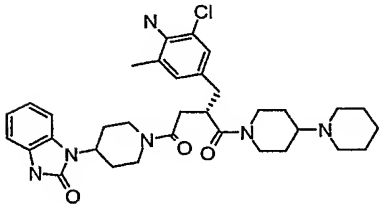
200 

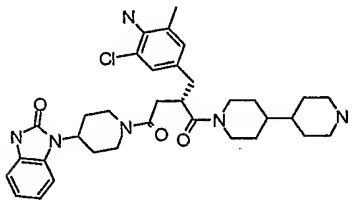
51 

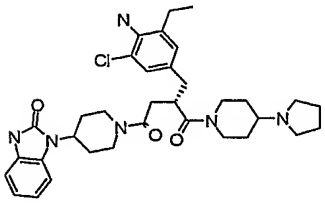
52 

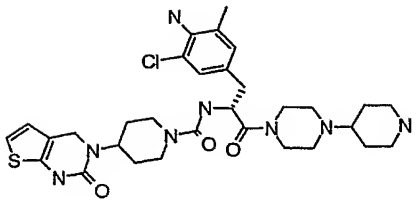
53 

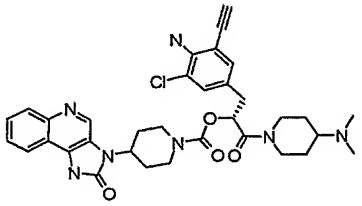
54 

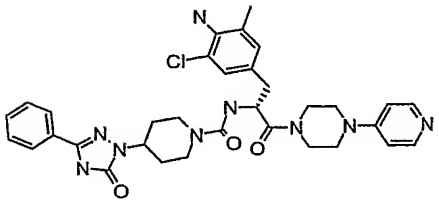
55 

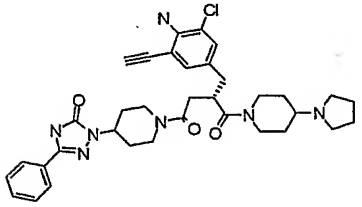
56 

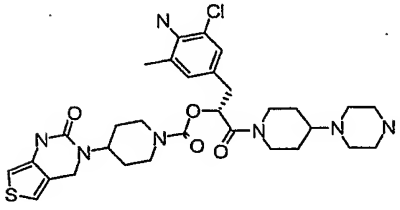
57 

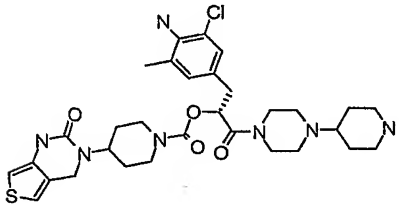
201 

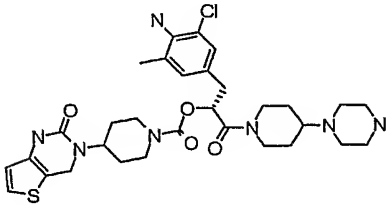
202 

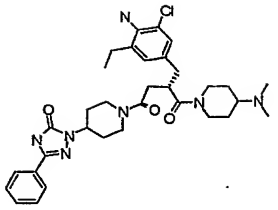
203 

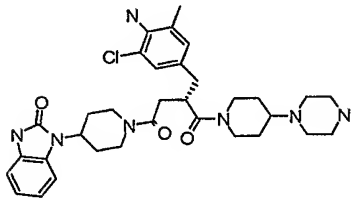
204 

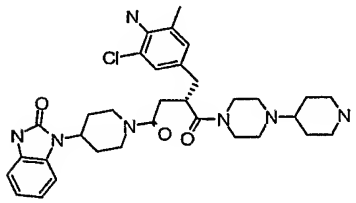
205 

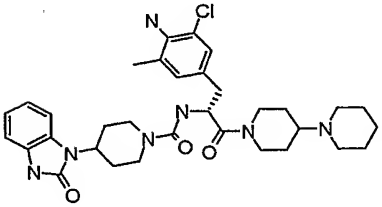
206 

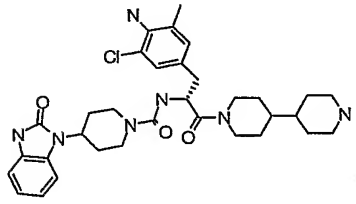
207 

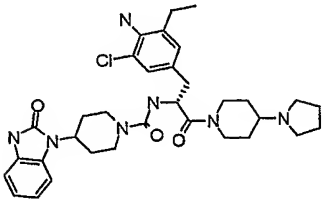
58 

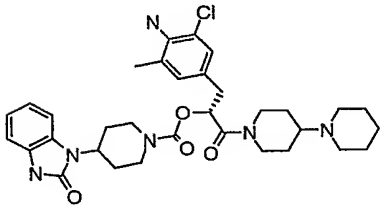
59 

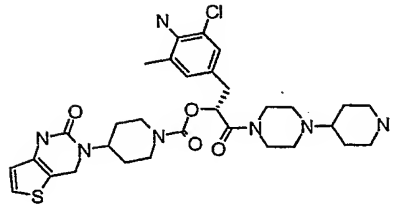
60 

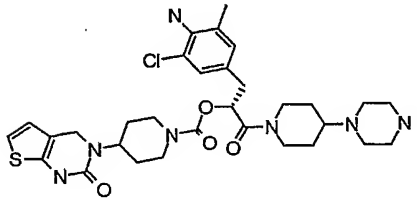
61 

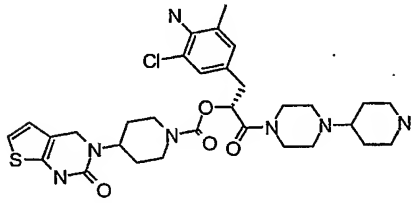
62 

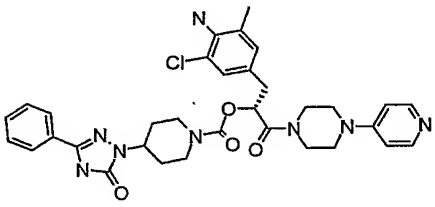
63 

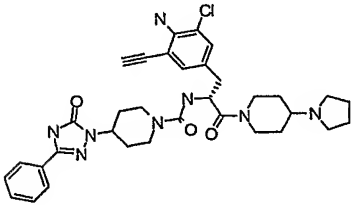
64 

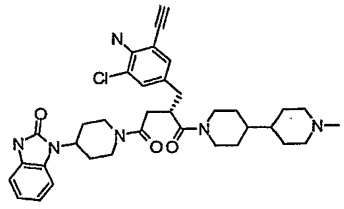
208 

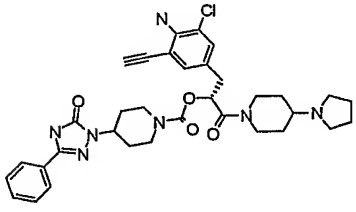
209 

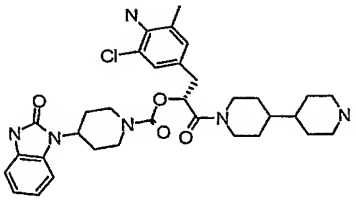
210 

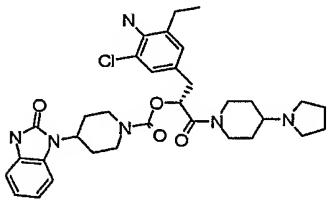
211 

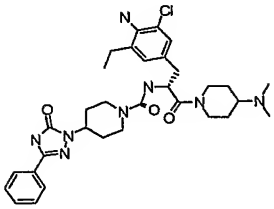
212 

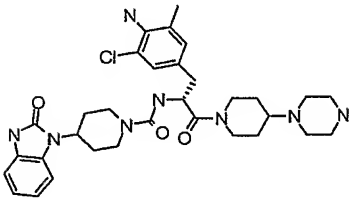
213 

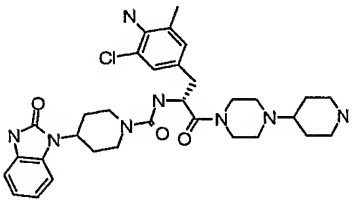
214 

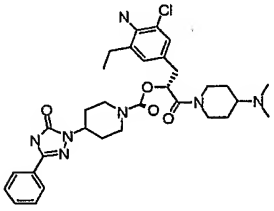
65 

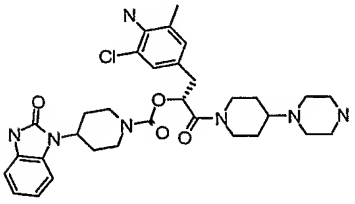
66 

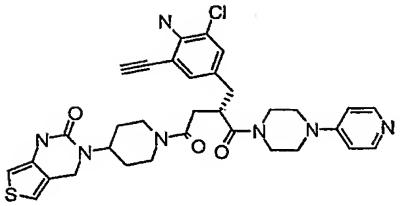
67 

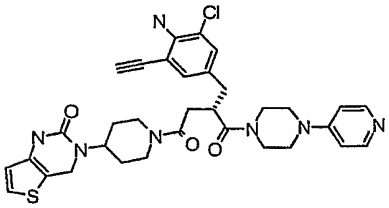
68 

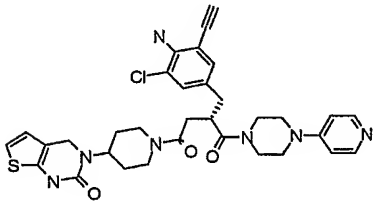
69 

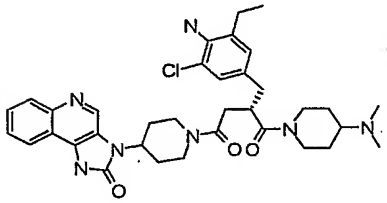
70 

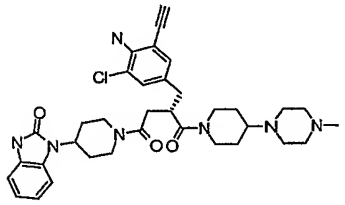
71 

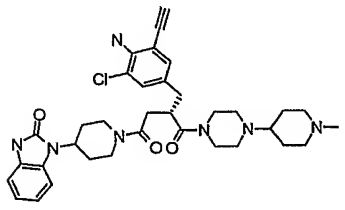
215 

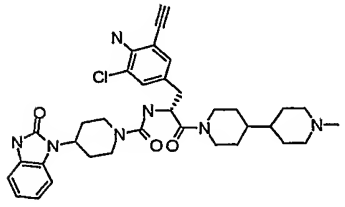
216 

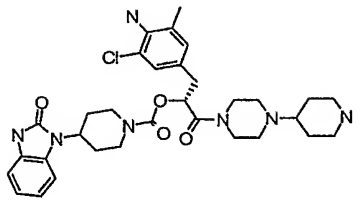
217 

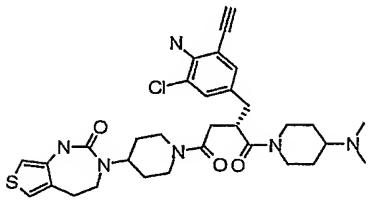
218 

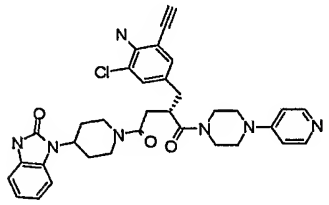
219 

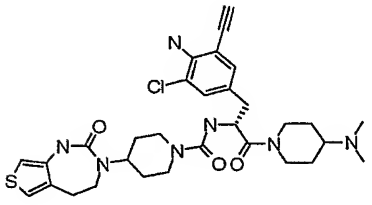
220 

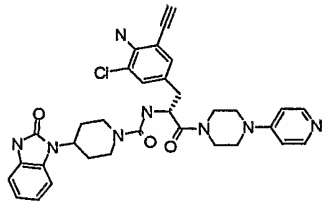
221 

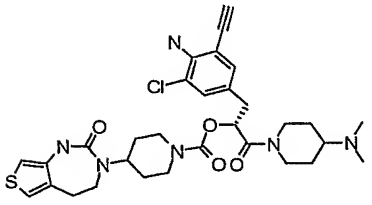
72 

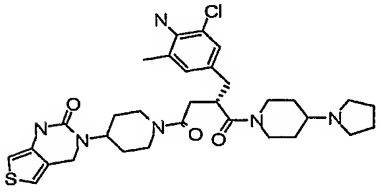
73 

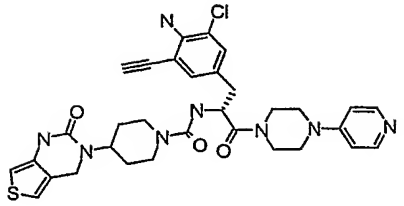
74 

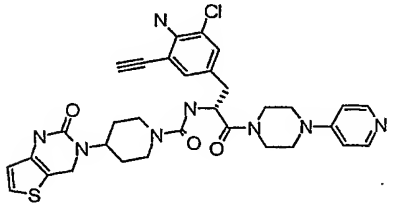
75 

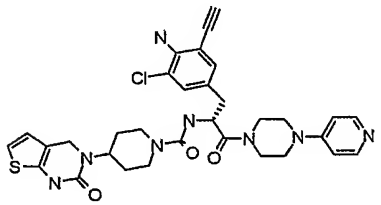
76 

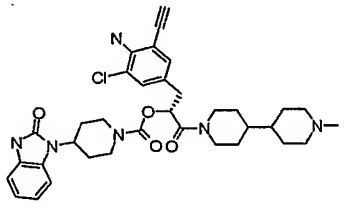
77 

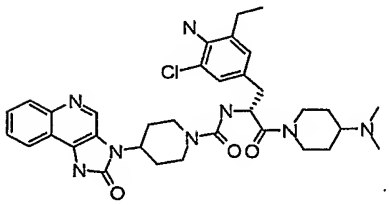
78 

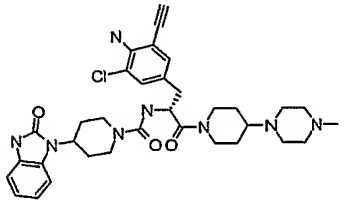
222 

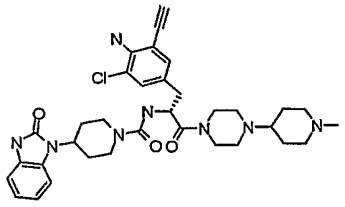
223 

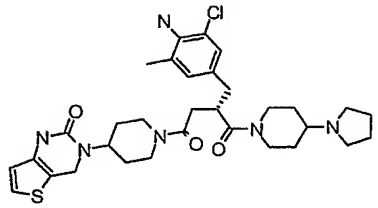
224 

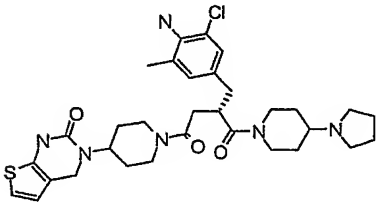
225 

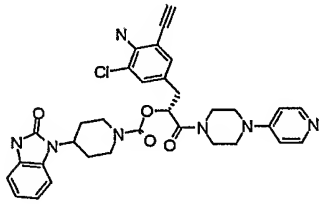
226 

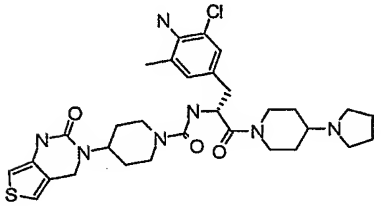
227 

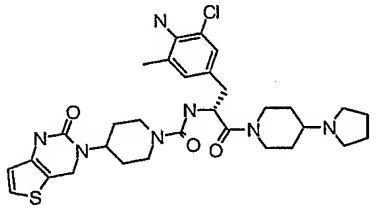
228 

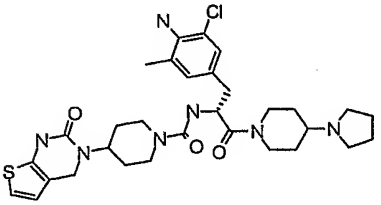
79 

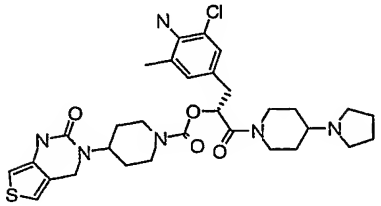
80 

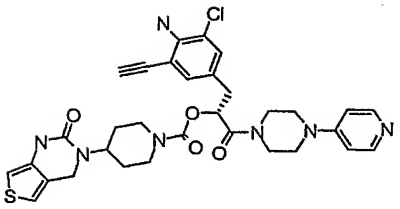
81 

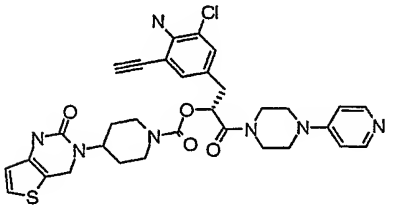
82 

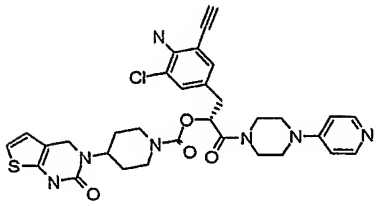
83 

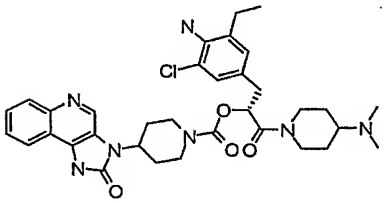
84 

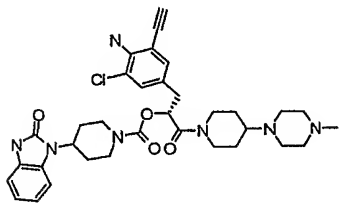
85 

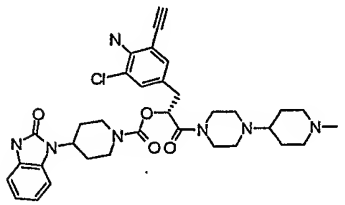
229 

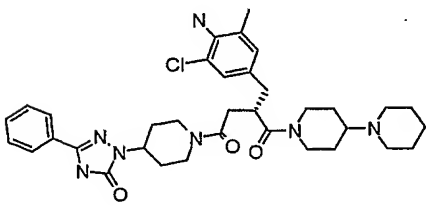
230 

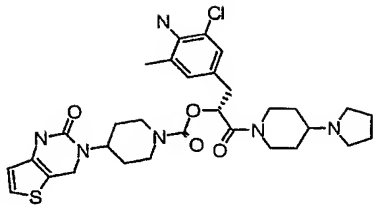
231 

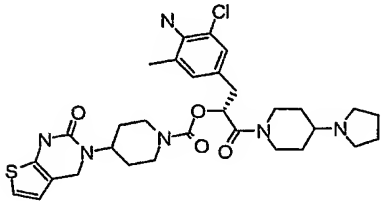
232 

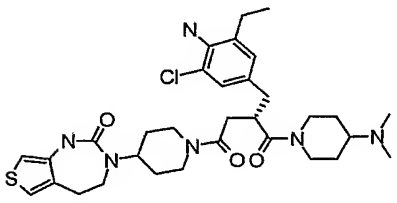
233 

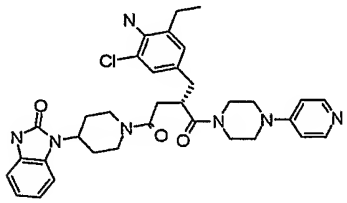
234 

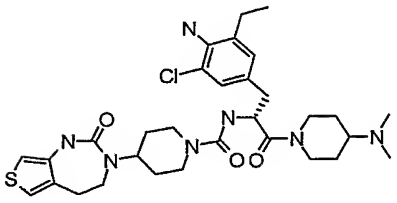
235 

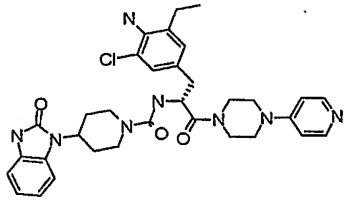
86 

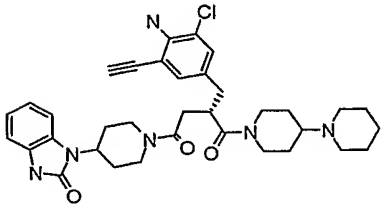
87 

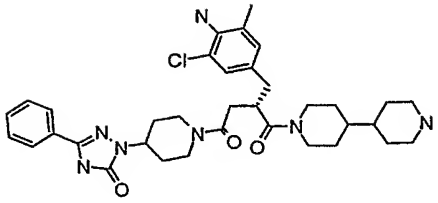
88 

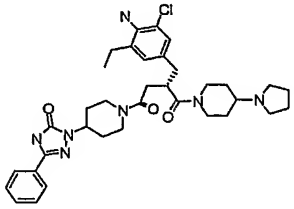
89 

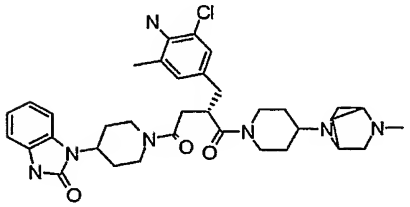
90 

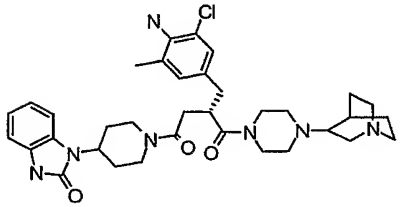
91 

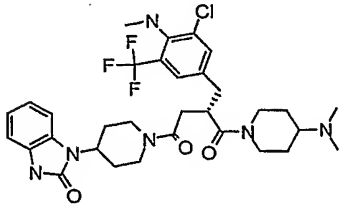
92 

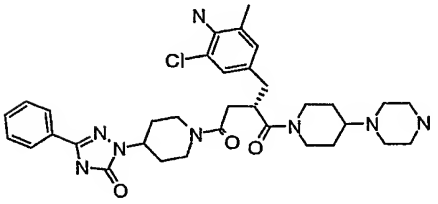
236 

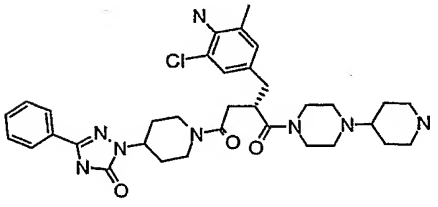
237 

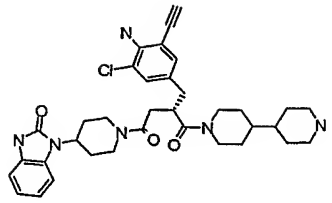
238 

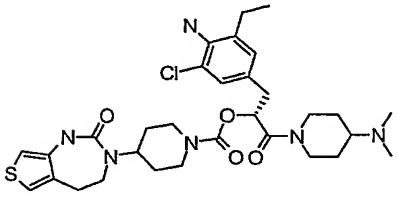
239 

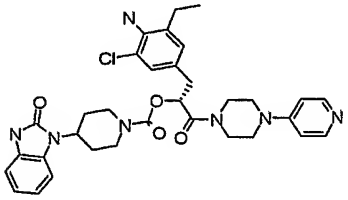
240 

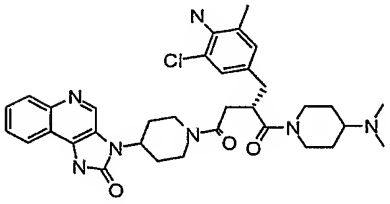
241 

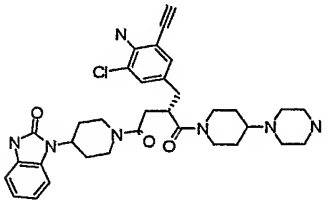
242 

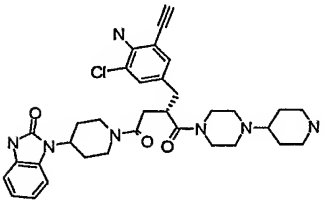
93 

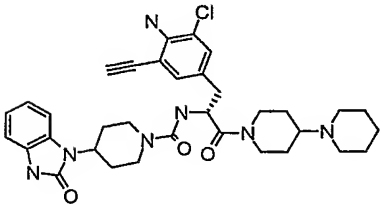
94 

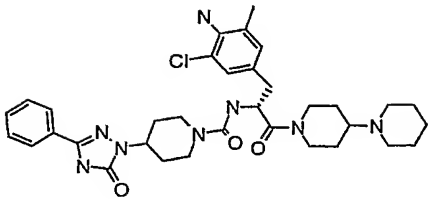
95 

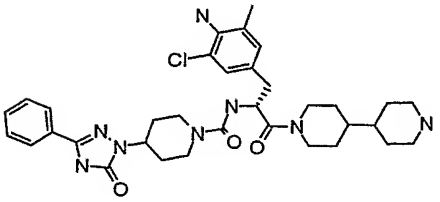
96 

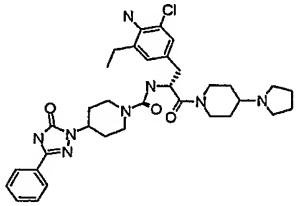
97 

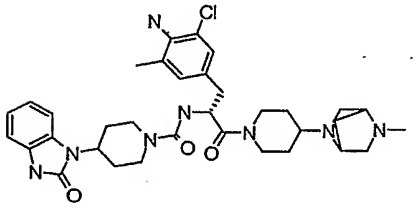
98 

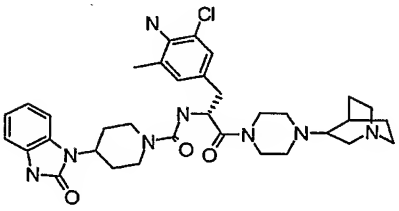
99 

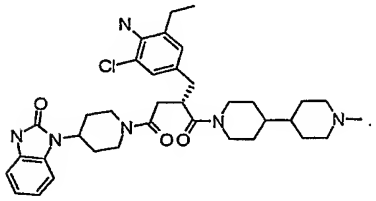
243 

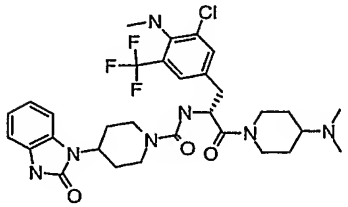
244 

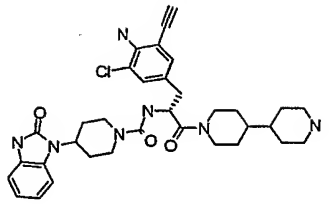
245 

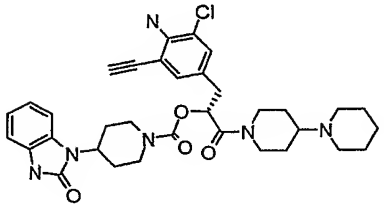
246 

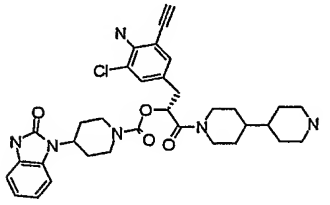
247 

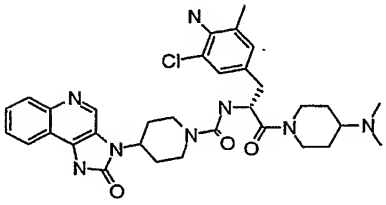
248 

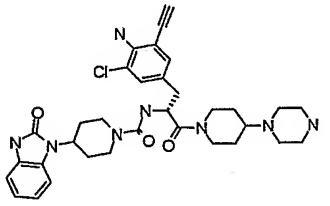
249 

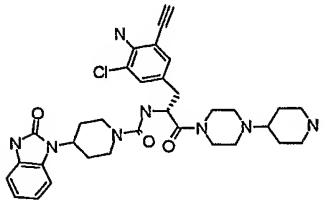
100 

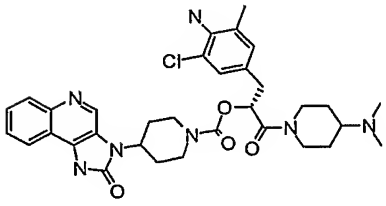
101 

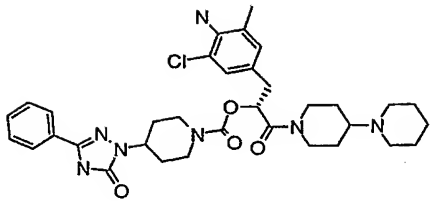
102 

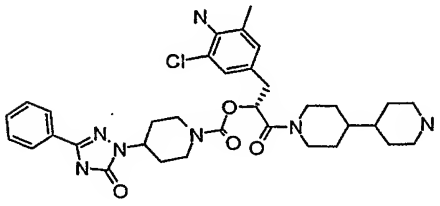
103 

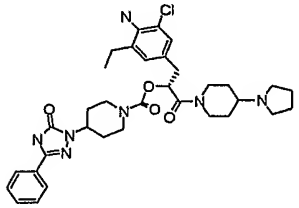
104 

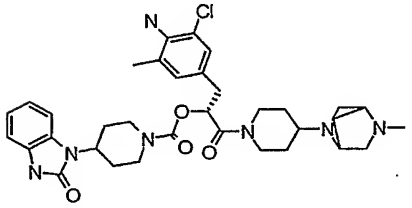
105 

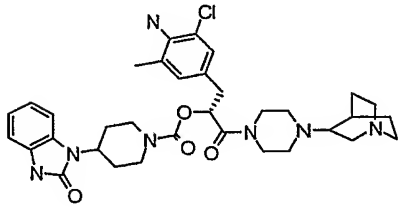
106 

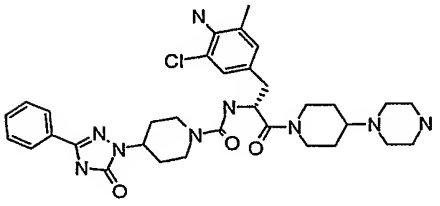
250 

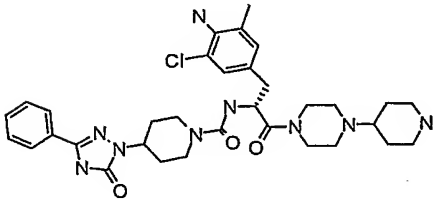
251 

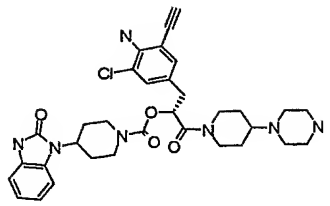
252 

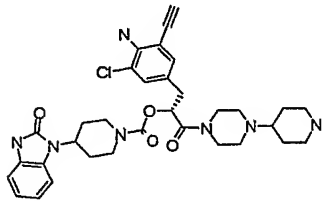
253 

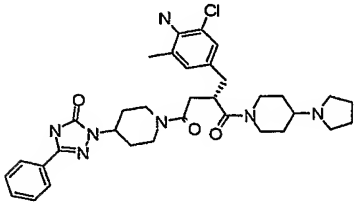
254 

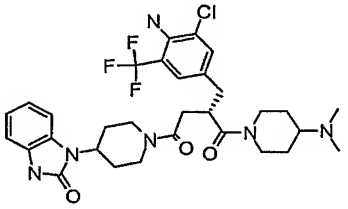
255 

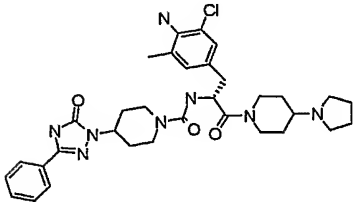
256 

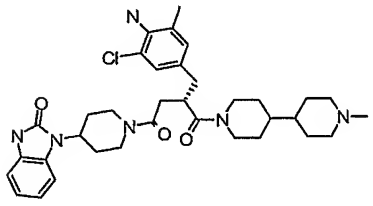
107 

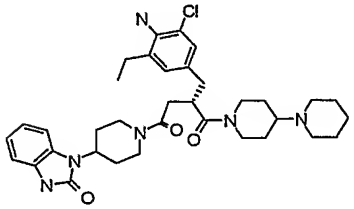
108 

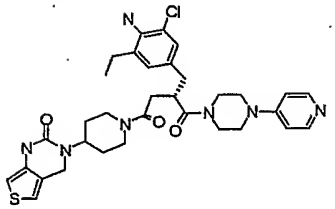
109 

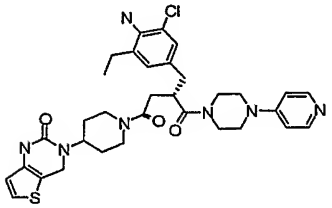
110 

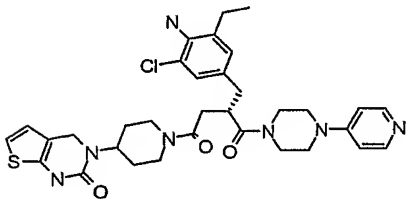
111 

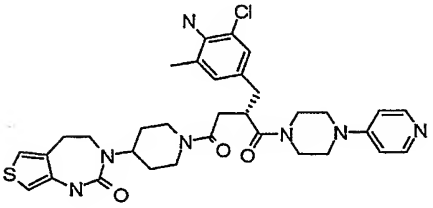
112 

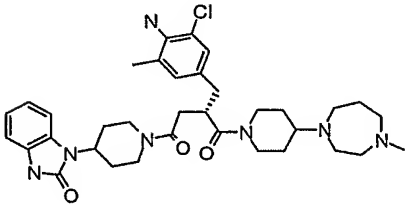
113 

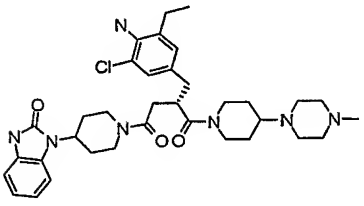
257 

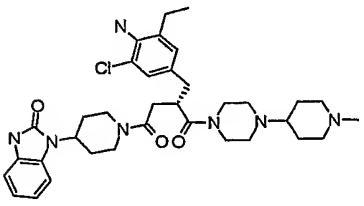
258 

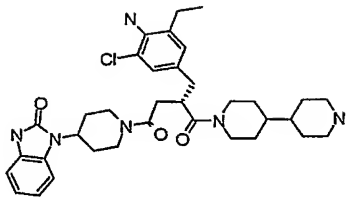
259 

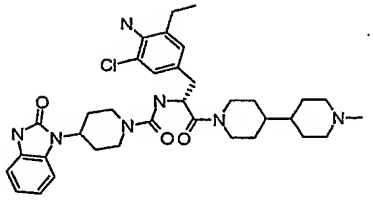
260 

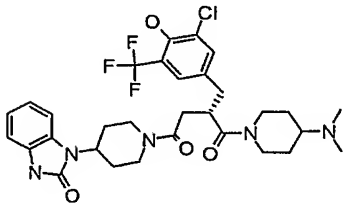
261 

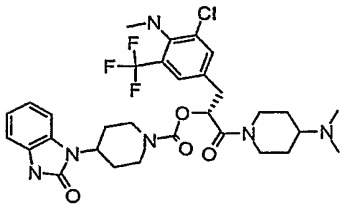
262 

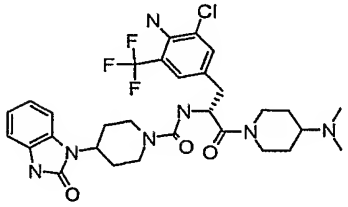
263 

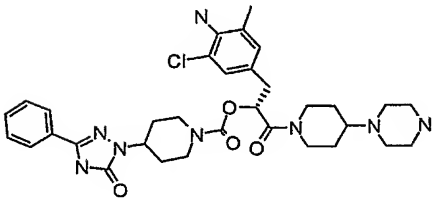
114 

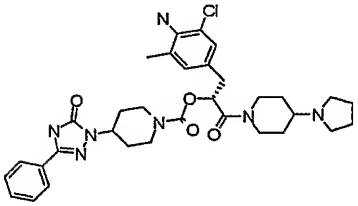
264 

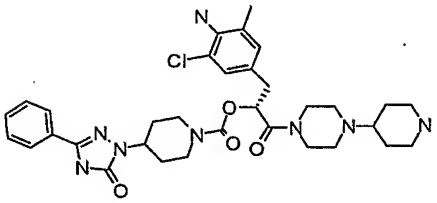
115 

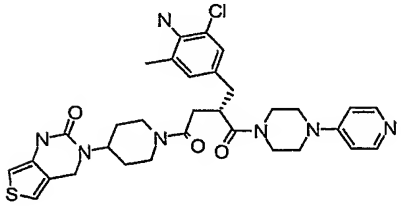
265 

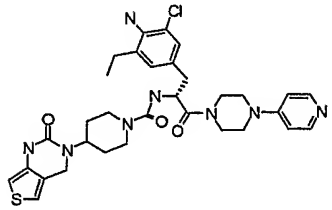
116 

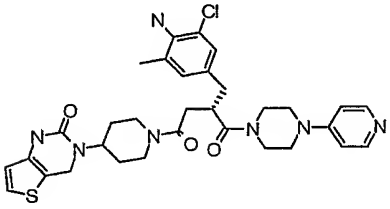
266 

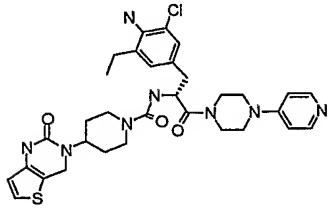
117 

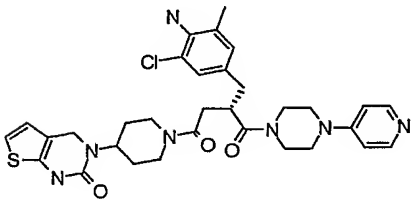
267 

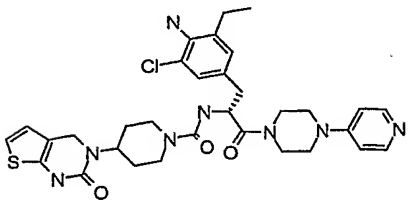
118 

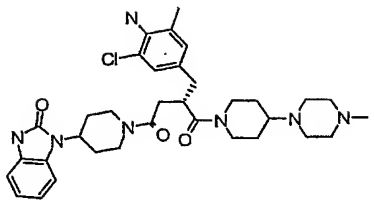
268 

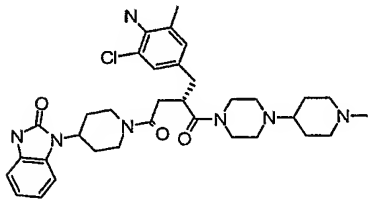
119 

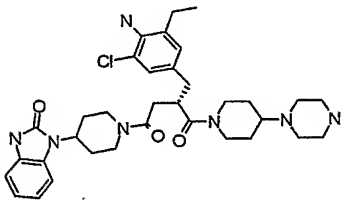
269 

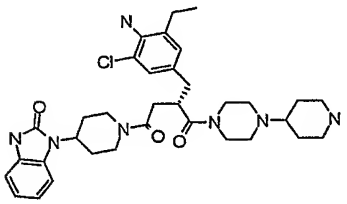
120 

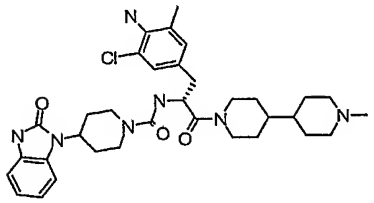
270 

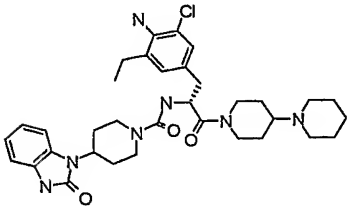
121 

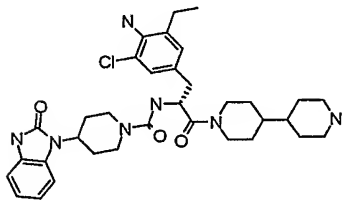
122 

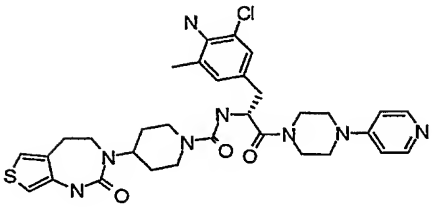
123 

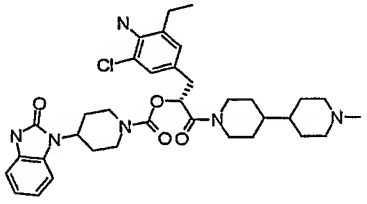
124 

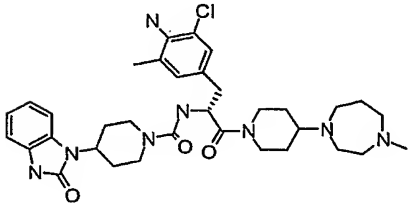
125 

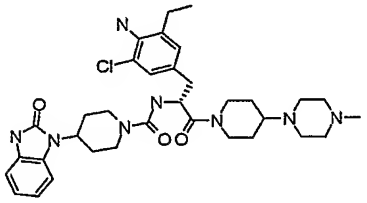
126 

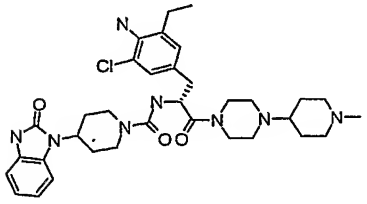
127 

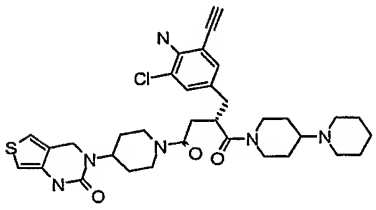
271 

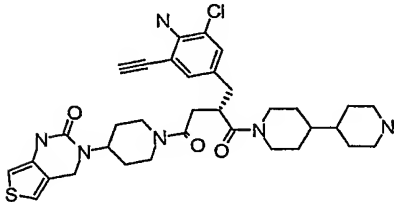
272 

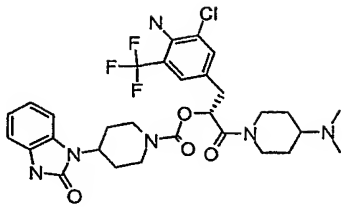
273 

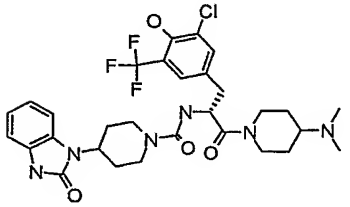
274 

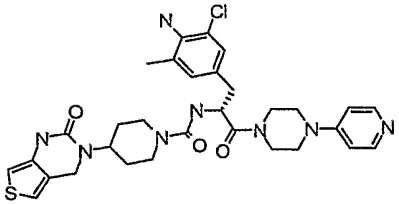
275 

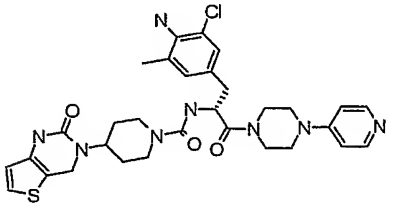
276 

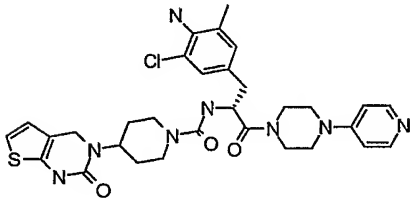
277 

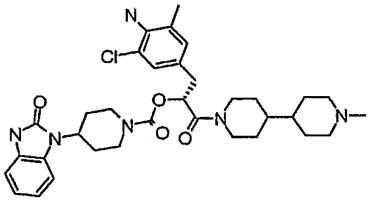
128 

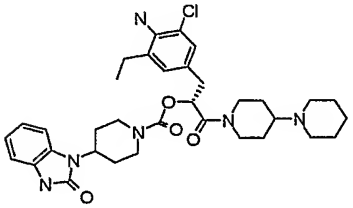
129 

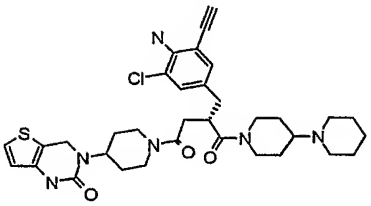
130 

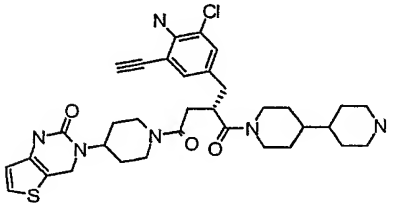
131 

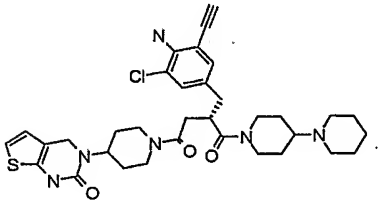
132 

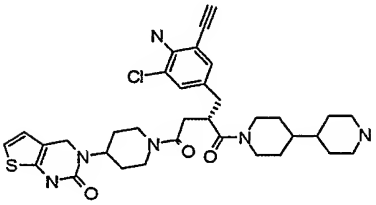
133 

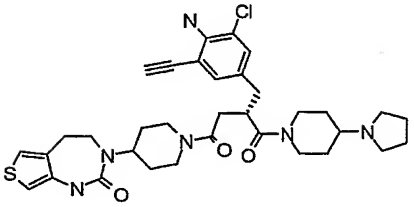
134 

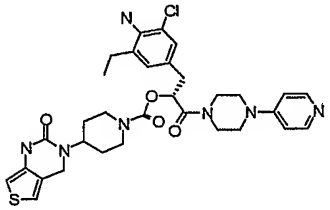
278 

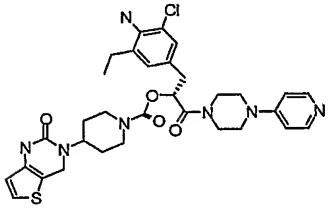
279 

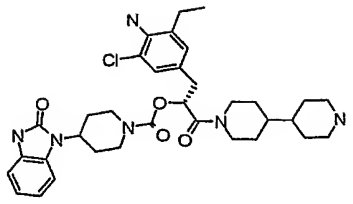
280 

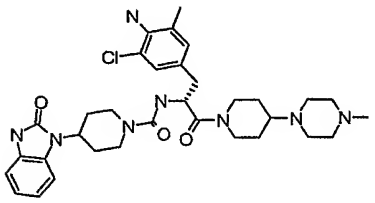
281 

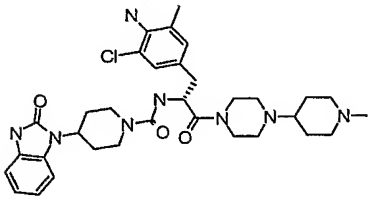
282 

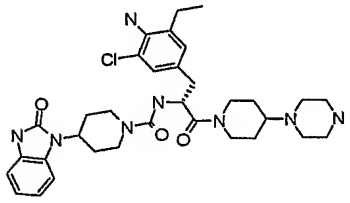
283 

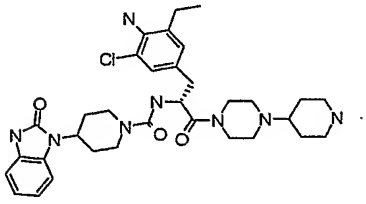
284 

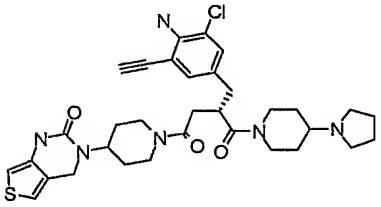
135 

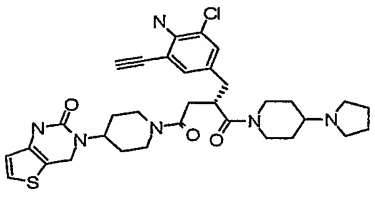
136 

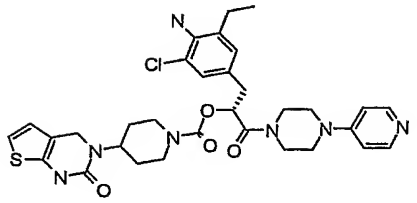
137 

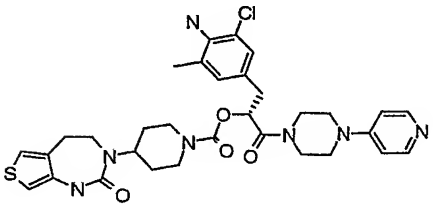
138 

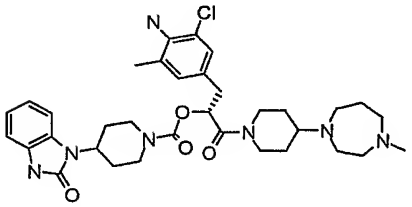
139 

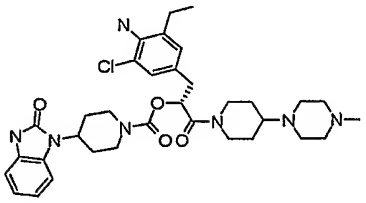
140 

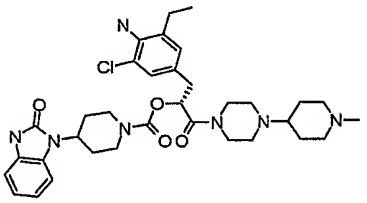
141 

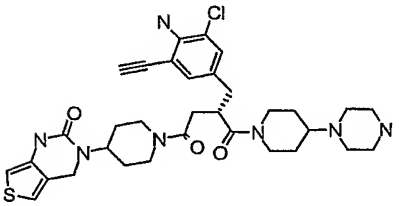
285 

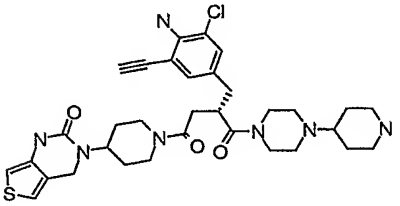
286 

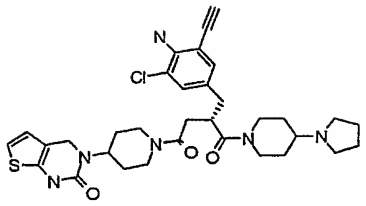
287 

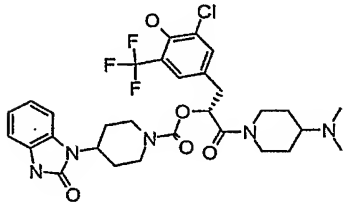
288 

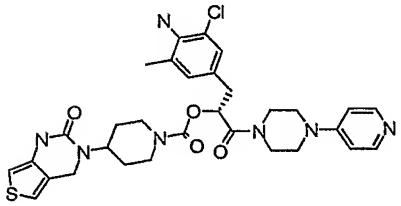
289 

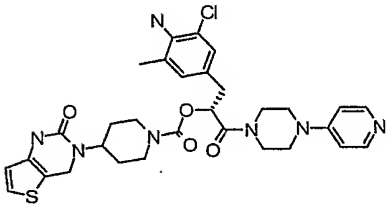
290 

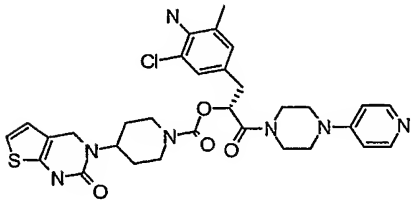
291 

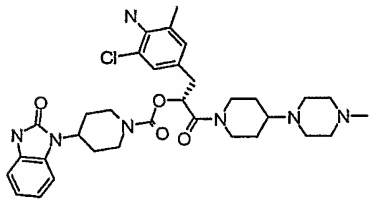
142 

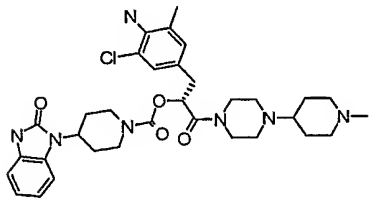
143 

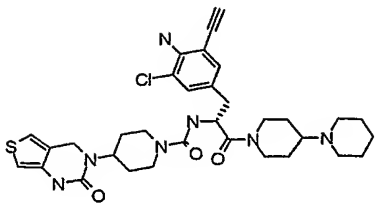
144 

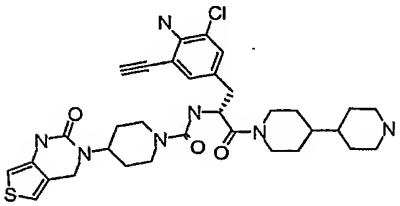
145 

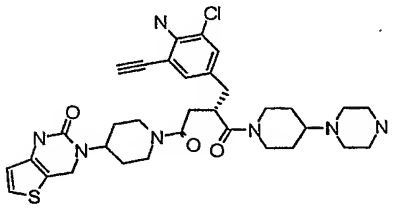
146 

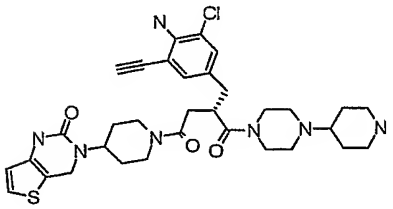
147 

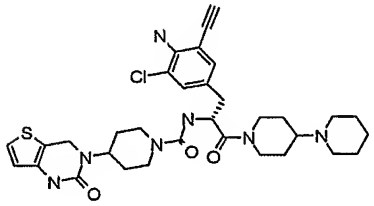
148 

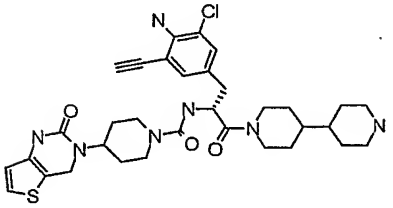
292 

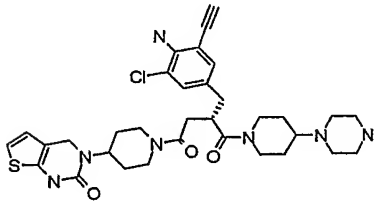
293 

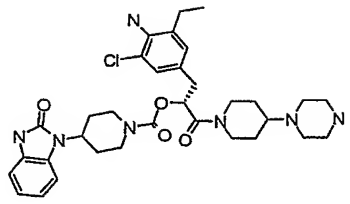
294 

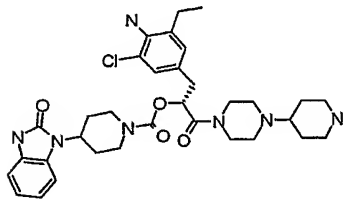
295 

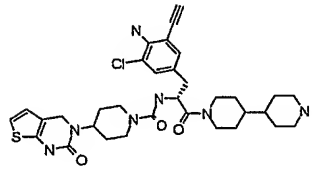
296 

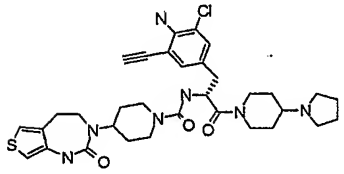
297 

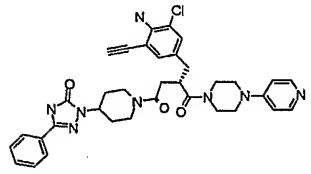
298 

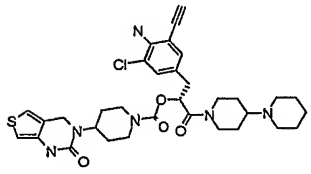
149 

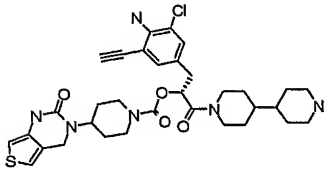
150 

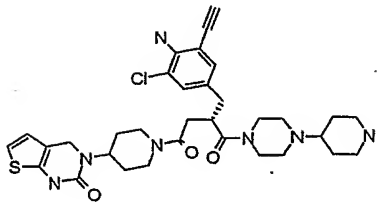
301 

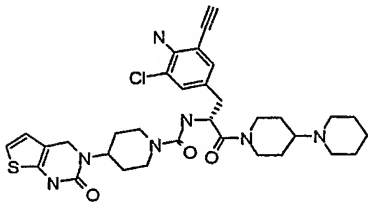
302 

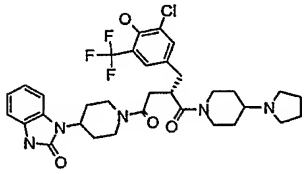
303 

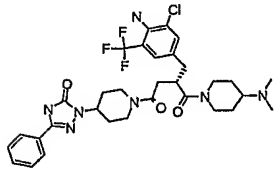
304 

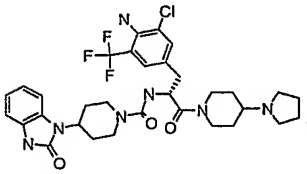
305 

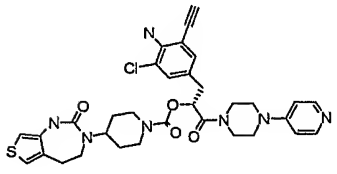
299 

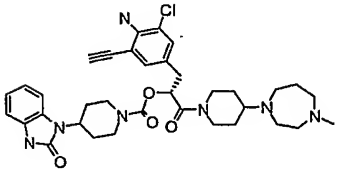
300 

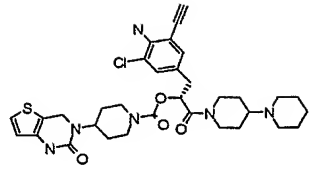
451 

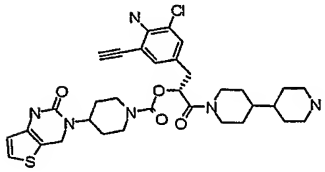
452 

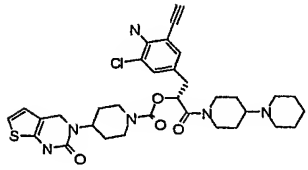
453 

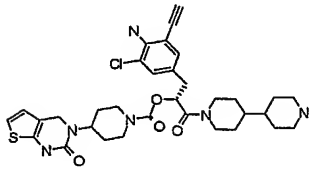
454 

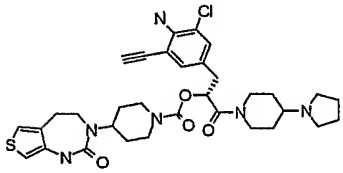
455 

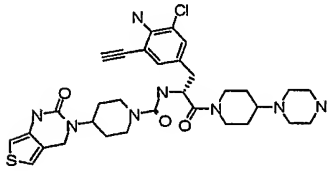
306 

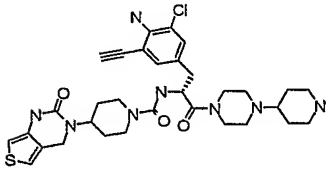
307 

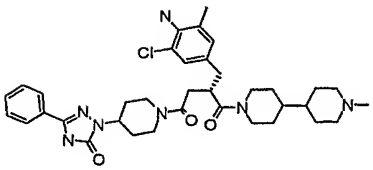
308 

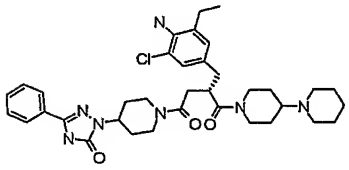
309 

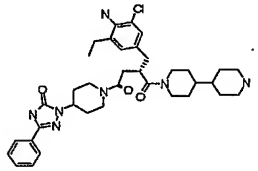
310 

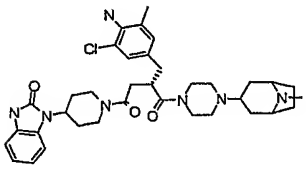
311 

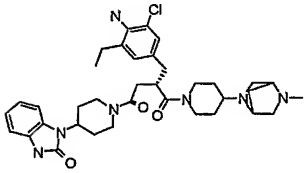
312 

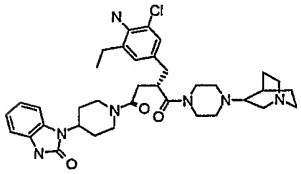
456 

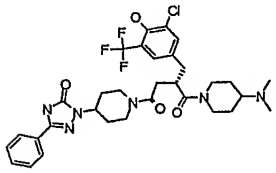
457 

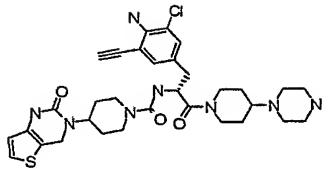
458 

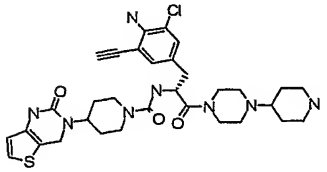
459 

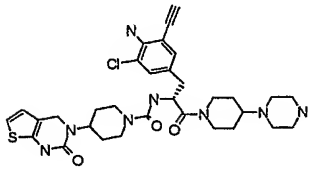
460 

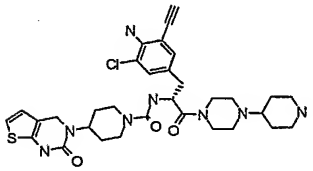
461 

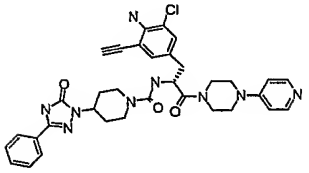
462 

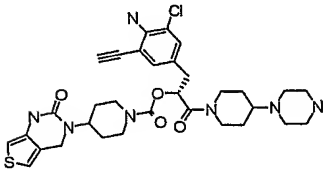
313 

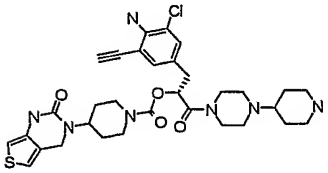
314 

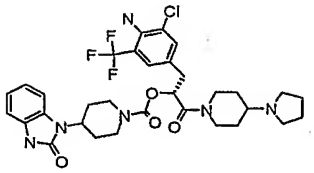
315 

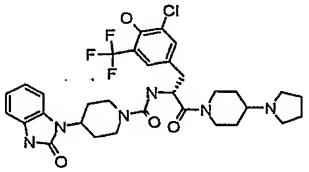
316 

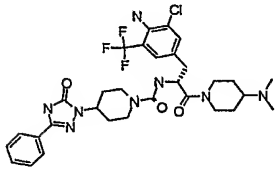
317 

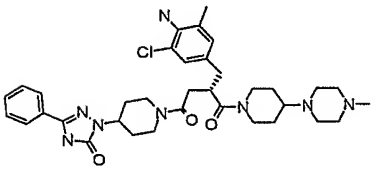
318 

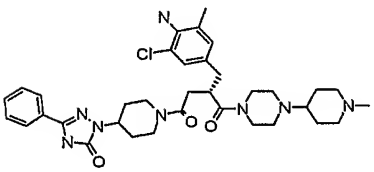
319 

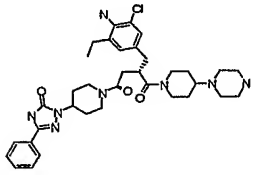
463 

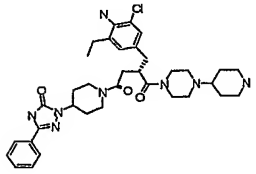
464 

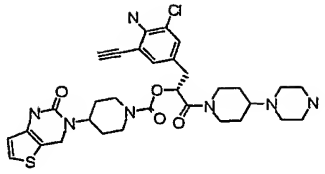
465 

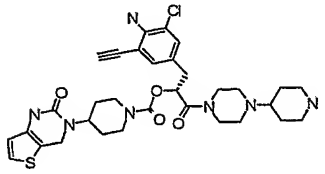
466 

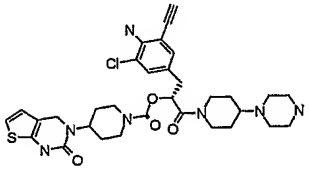
467 

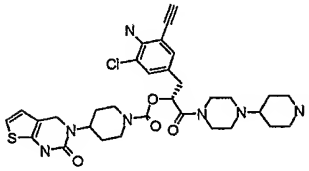
468 

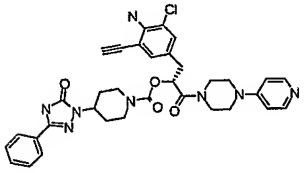
469 

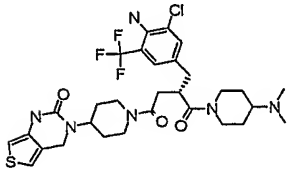
320 

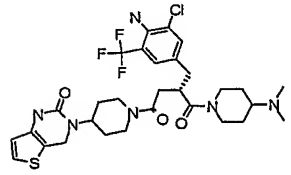
321 

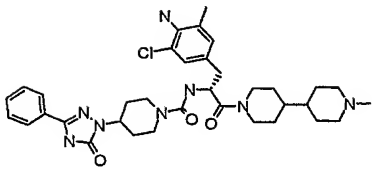
322 

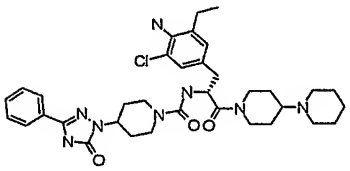
323 

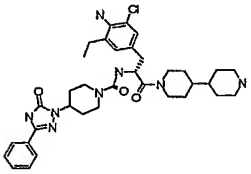
324 

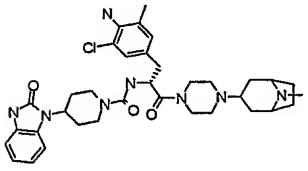
325 

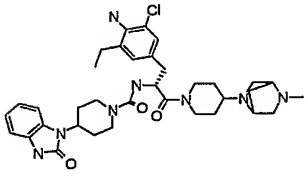
326 

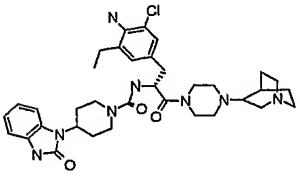
470 

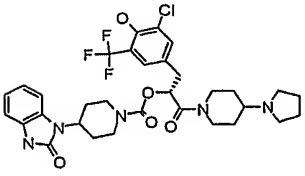
471 

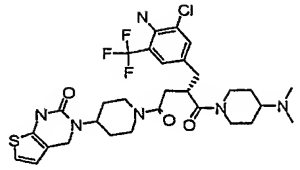
472 

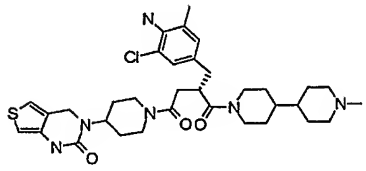
473 

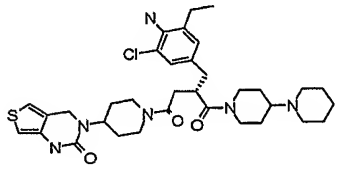
474 

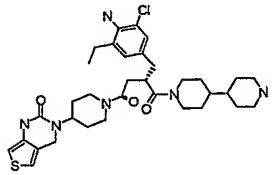
475 

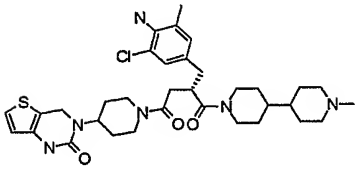
476 

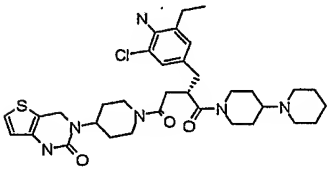
327 

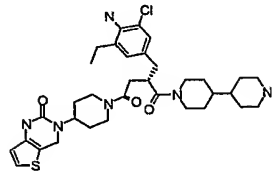
328 

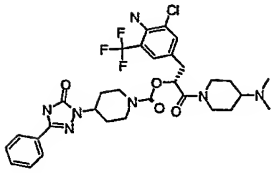
329 

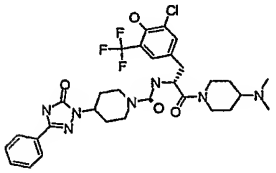
330 

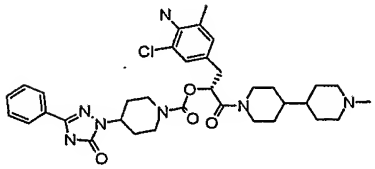
331 

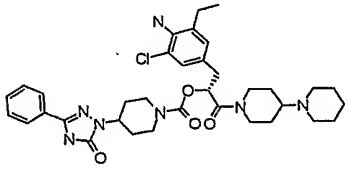
332 

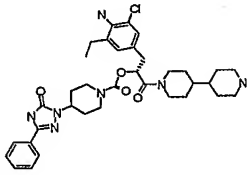
333 

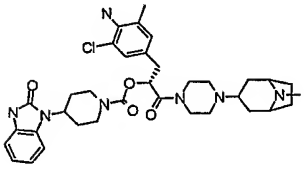
477 

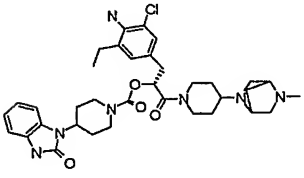
478 

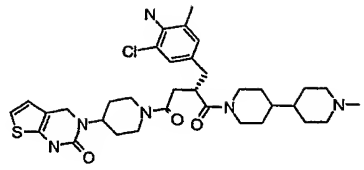
479 

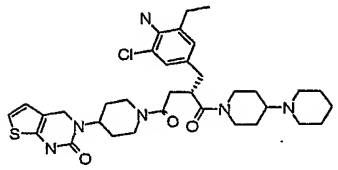
480 

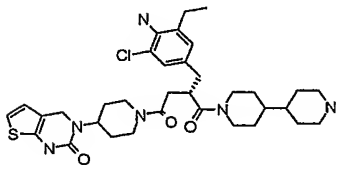
481 

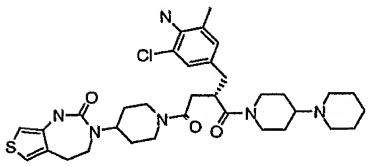
482 

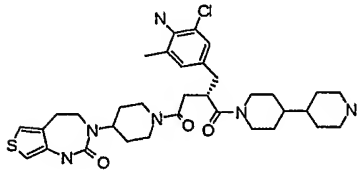
483 

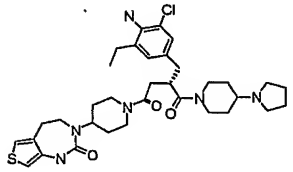
334 

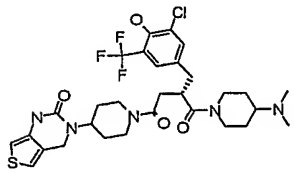
335 

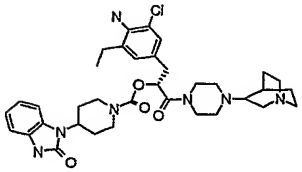
336 

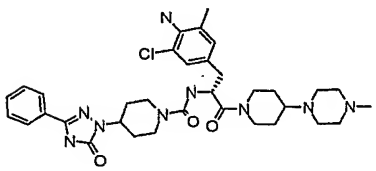
337 

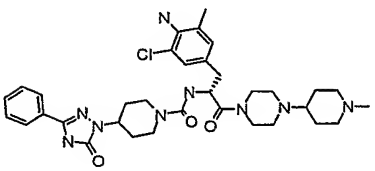
338 

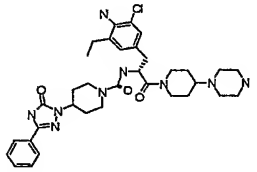
339 

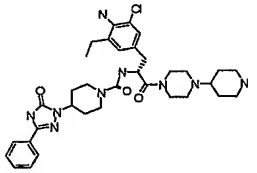
340 

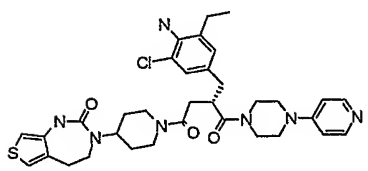
484 

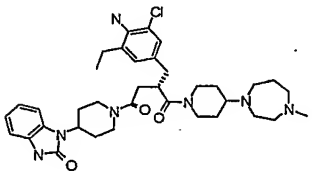
485 

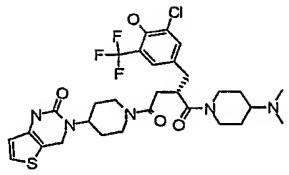
486 

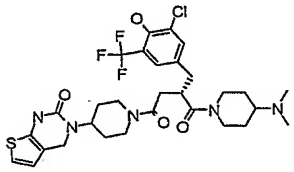
487 

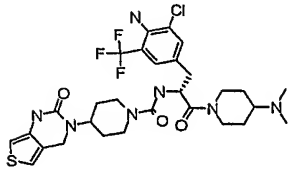
488 

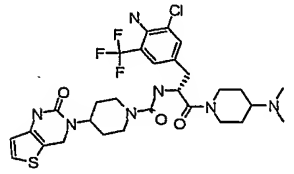
489 

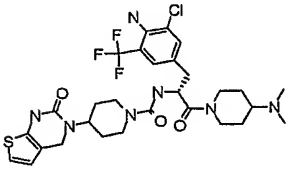
490 

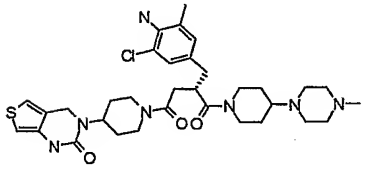
341 

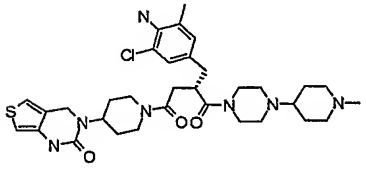
342 

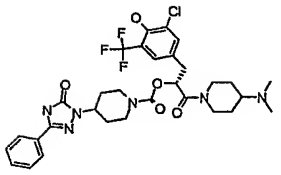
343 

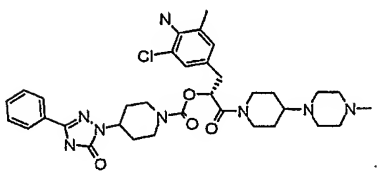
344 

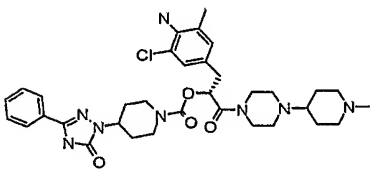
345 

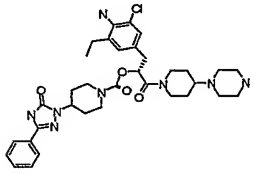
346 

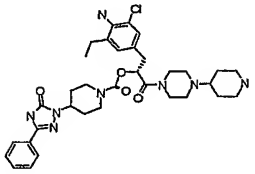
347 

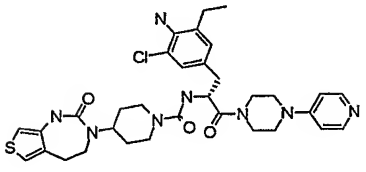
491 

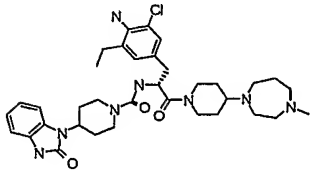
492 

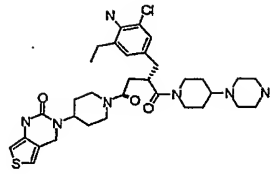
493 

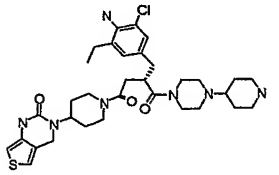
494 

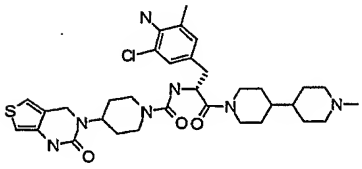
495 

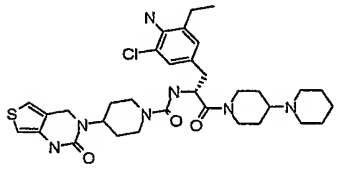
496 

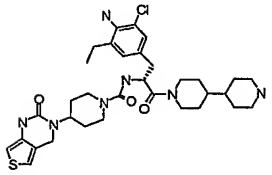
497 

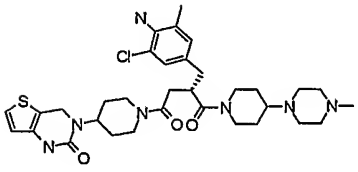
348 

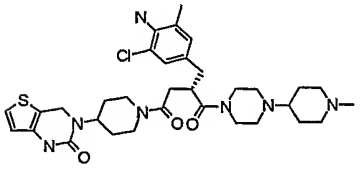
350 

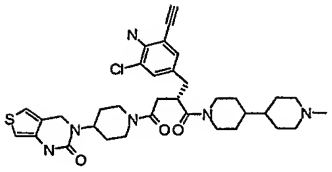
351 

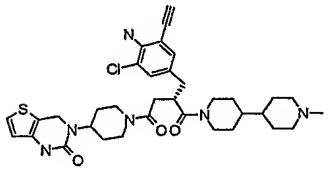
352 

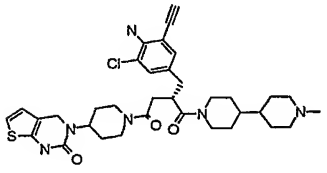
353 

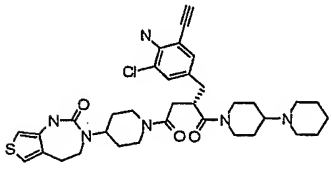
354 

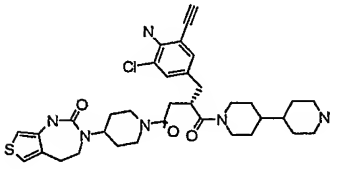
355 

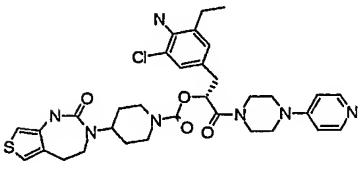
498 

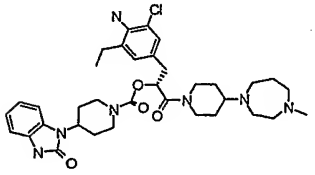
499 

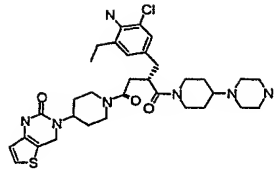
500 

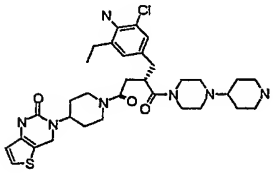
501 

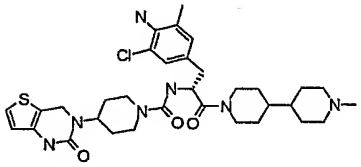
502 

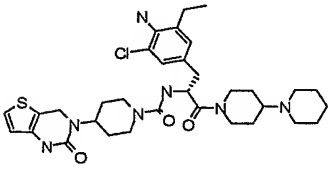
503 

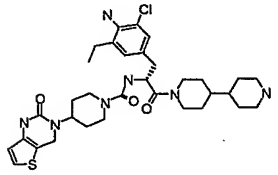
504 

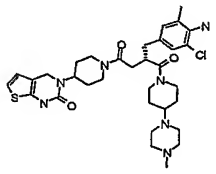
356 

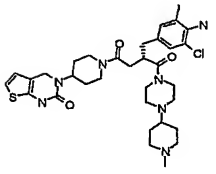
357 

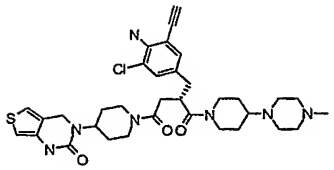
358 

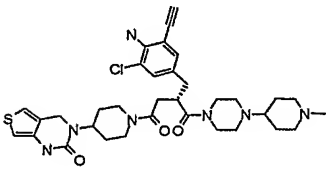
359 

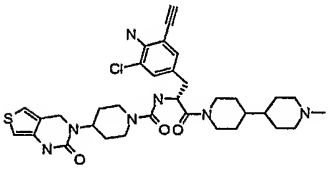
360 

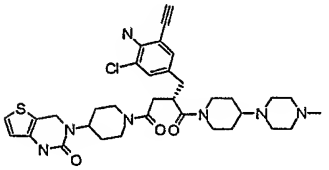
361 

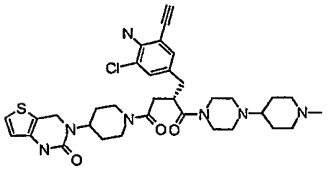
362 

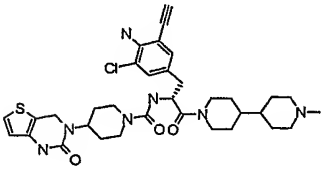
505 

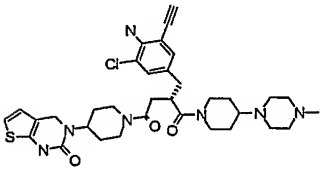
506 

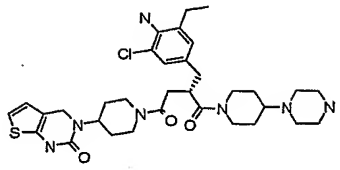
507 

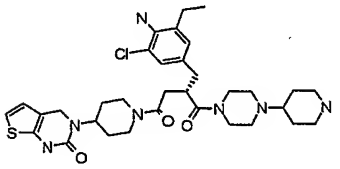
508 

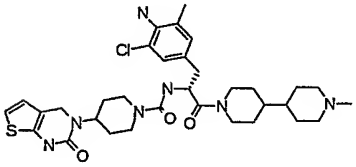
509 

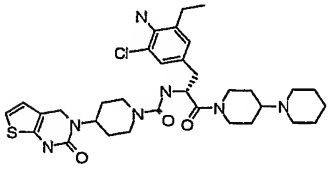
510 

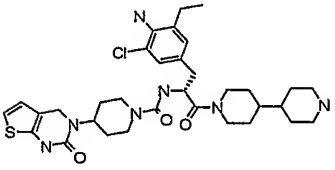
511 

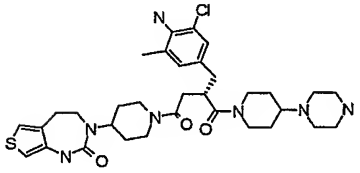
363 

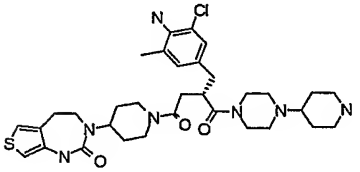
364 

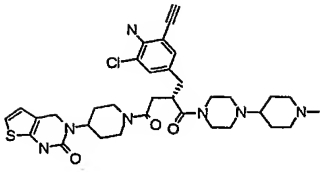
365 

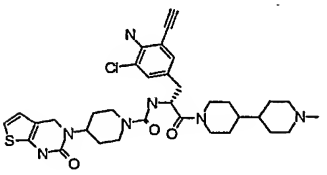
366 

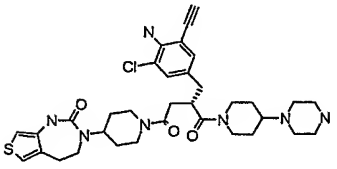
367 

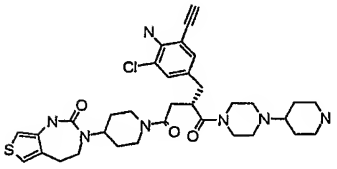
368 

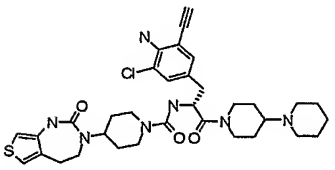
369 

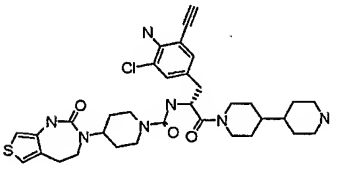
512 

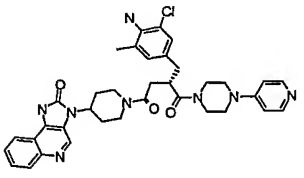
513 

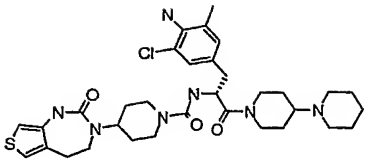
514 

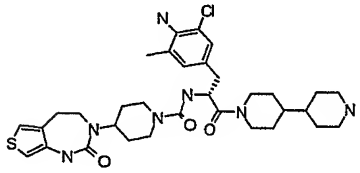
515 

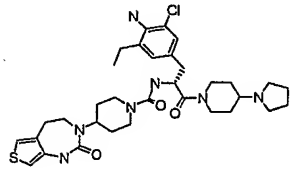
516 

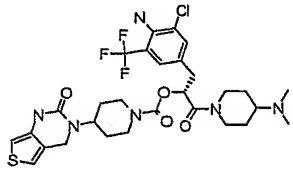
517 

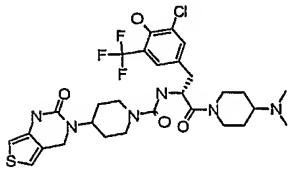
518 

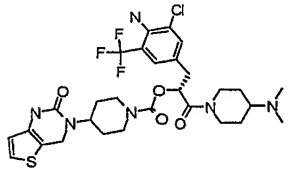
370 

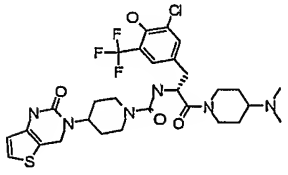
371 

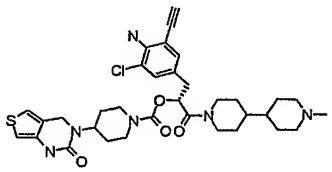
372 

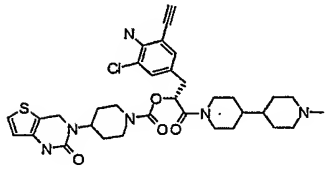
373 

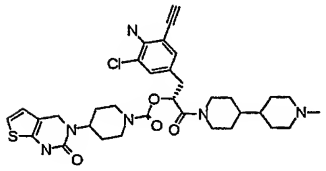
374 

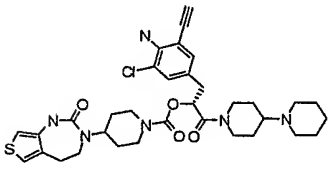
375 

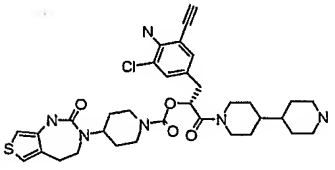
376 

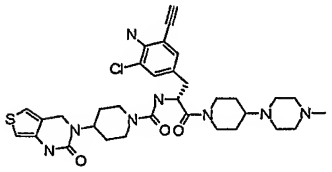
519 

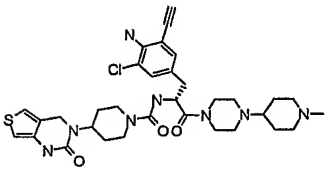
520 

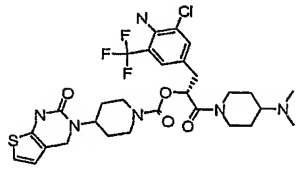
521 

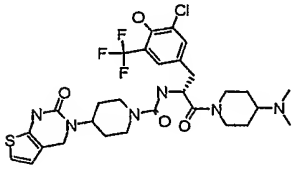
522 

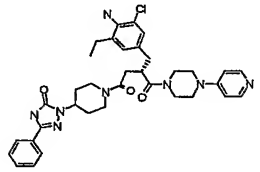
523 

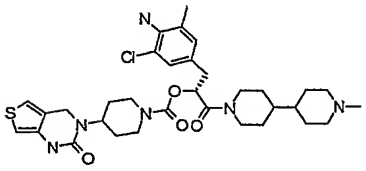
524 

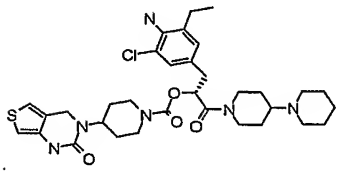
525 

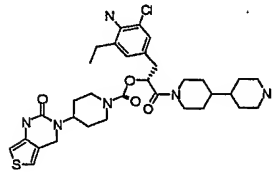
377 

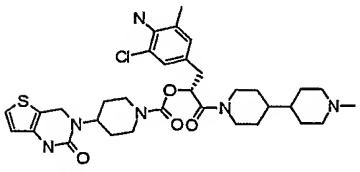
378 

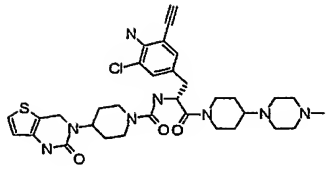
379 

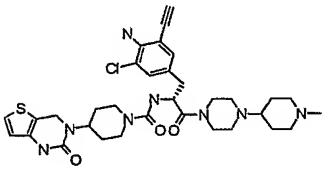
380 

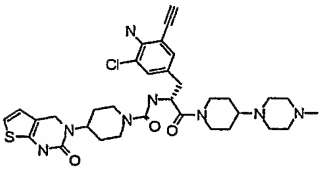
381 

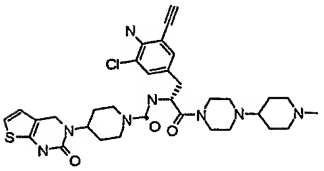
382 

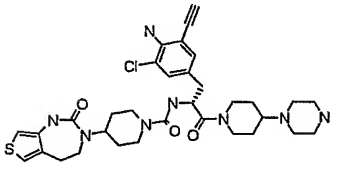
383 

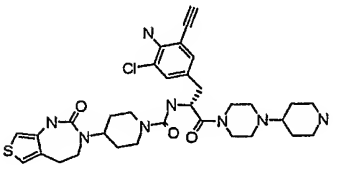
526 

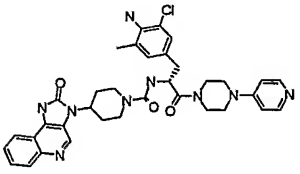
527 

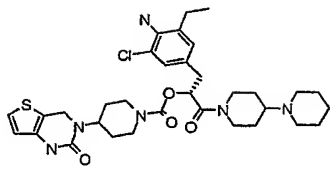
528 

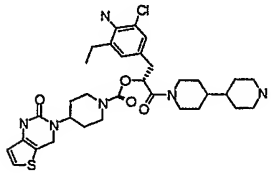
529 

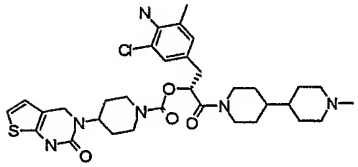
530 

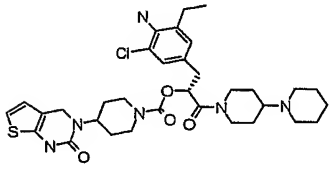
531 

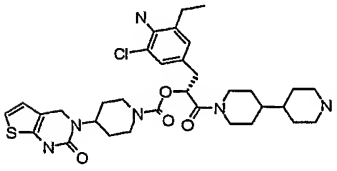
532 

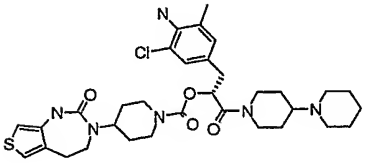
384 

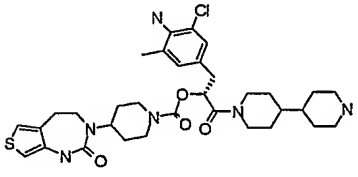
385 

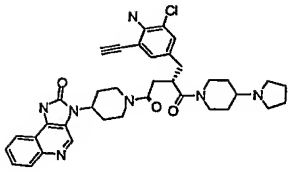
386 

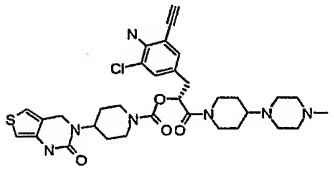
387 

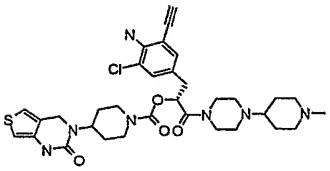
388 

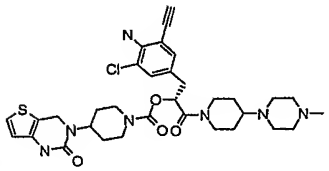
389 

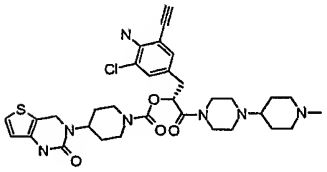
390 

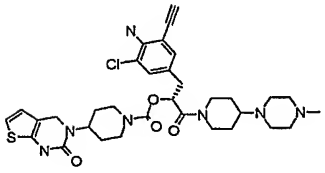
533 

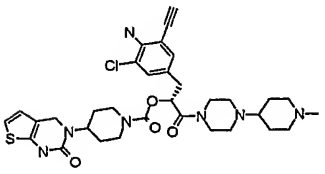
534 

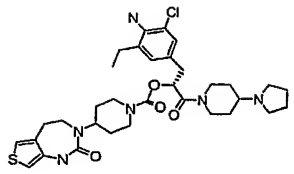
535 

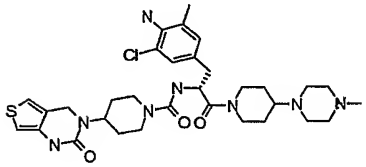
536 

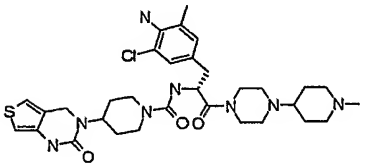
537 

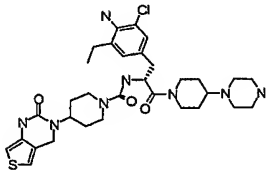
538 

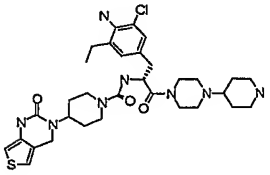
539 

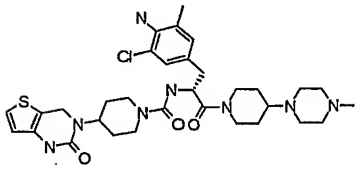
391 

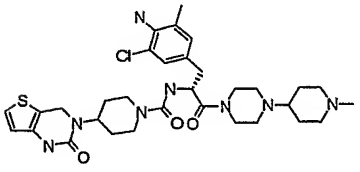
392 

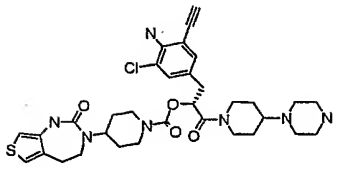
393 

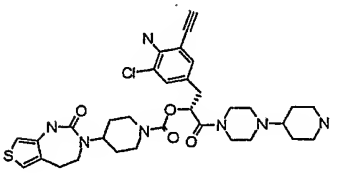
394 

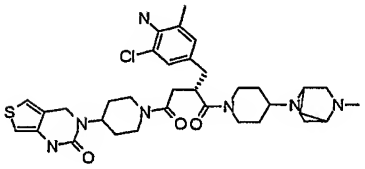
395 

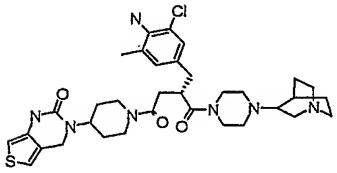
396 

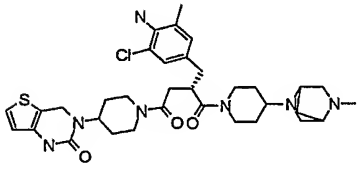
397 

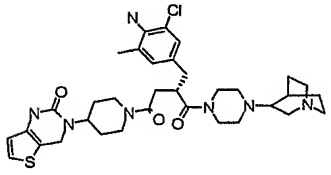
540 

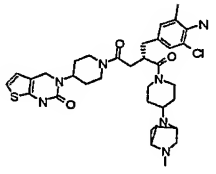
541 

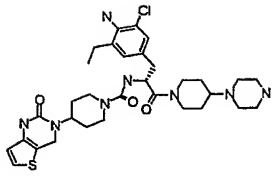
542 

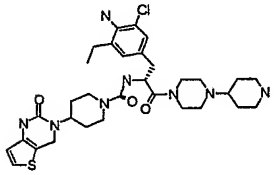
543 

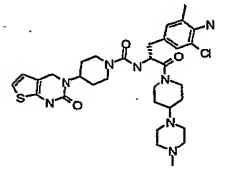
544 

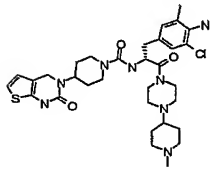
545 

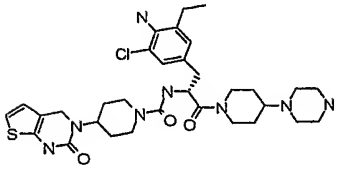
546 

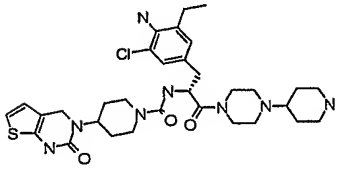
398 

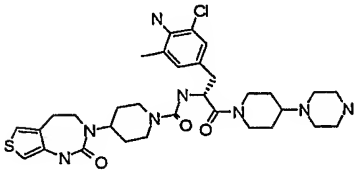
399 

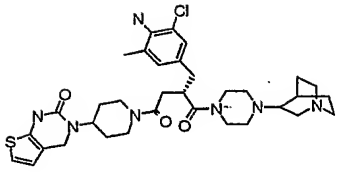
400 

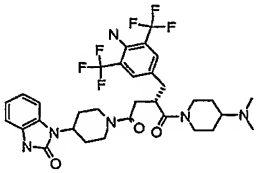
401 

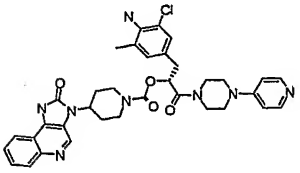
402 

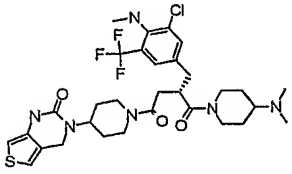
403 

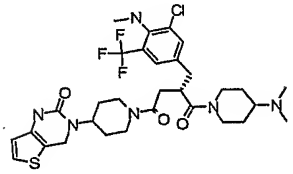
404 

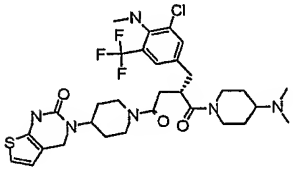
547 

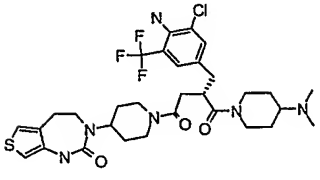
548 

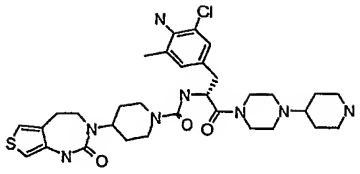
549 

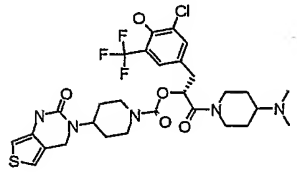
550 

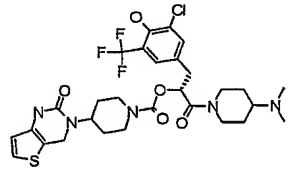
551 

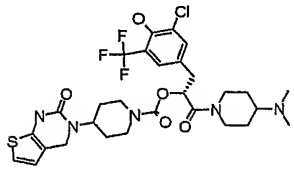
552 

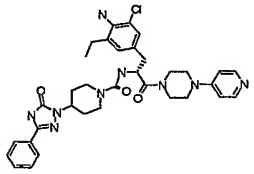
553 

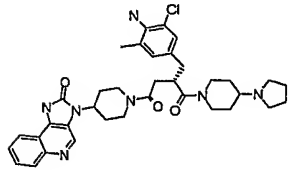
405 

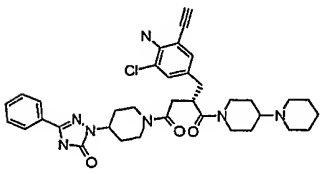
406 

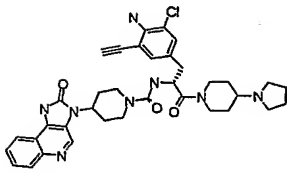
407 

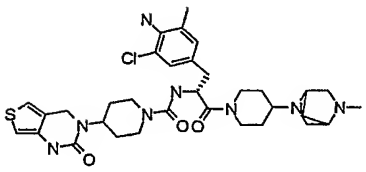
408 

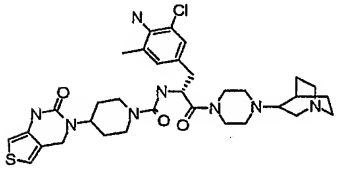
409 

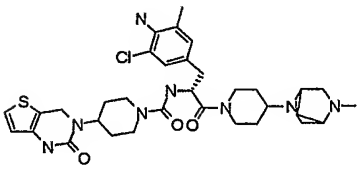
410 

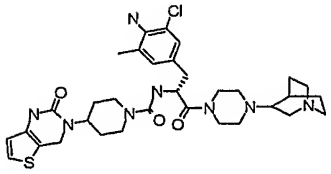
411 

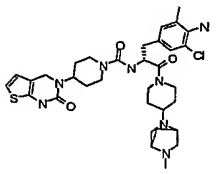
554 

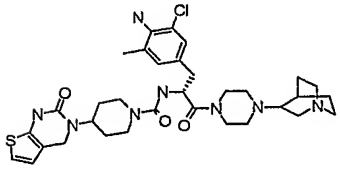
555 

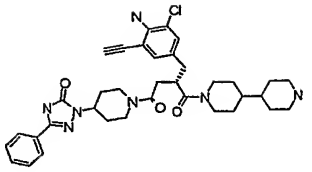
556 

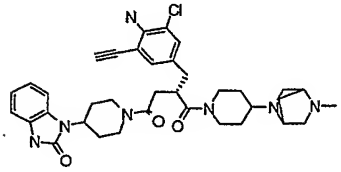
557 

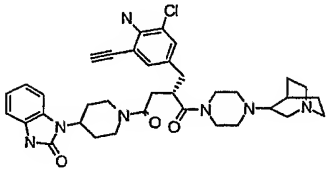
558 

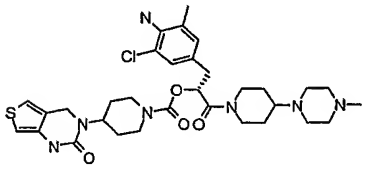
559 

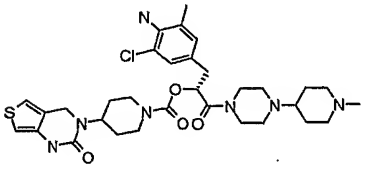
560 

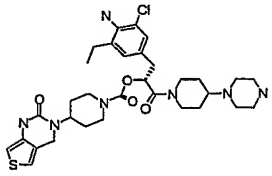
412 

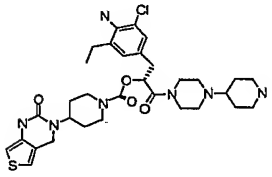
413 

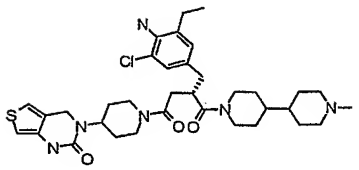
414 

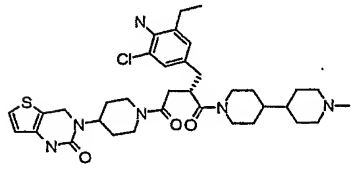
415 

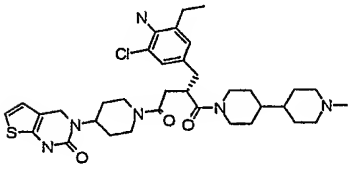
416 

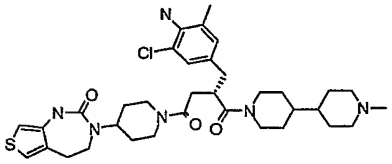
417 

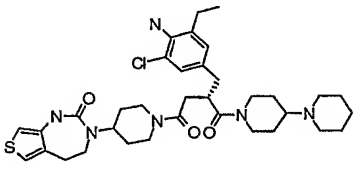
418 

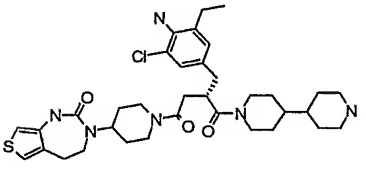
561 

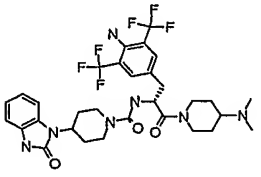
562 

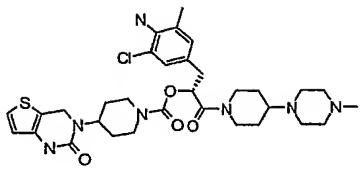
563 

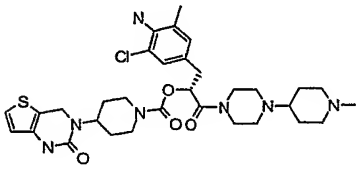
564 

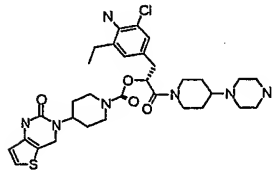
565 

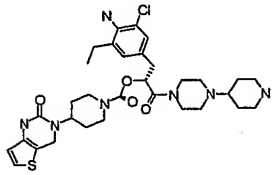
566 

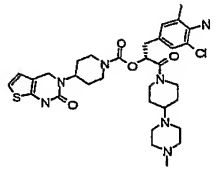
567 

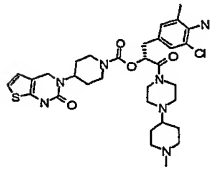
419 

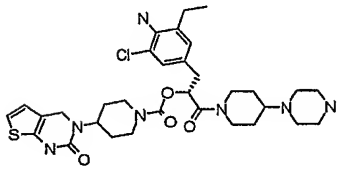
420 

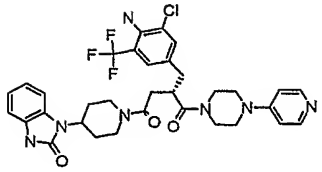
421 

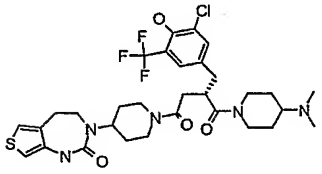
422 

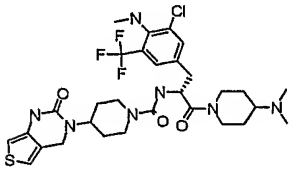
423 

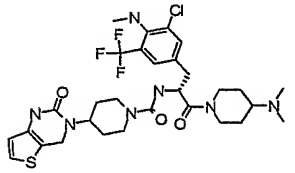
424 

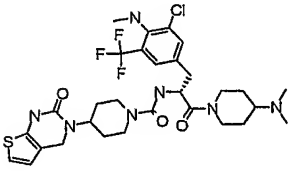
425 

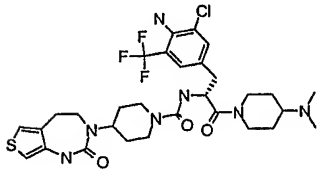
568 

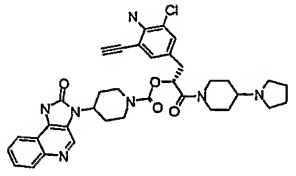
569 

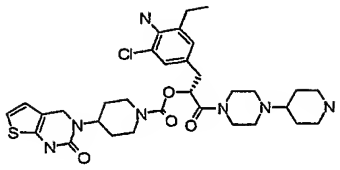
570 

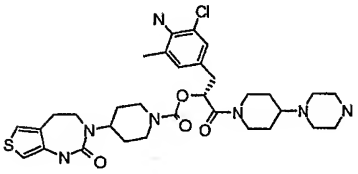
571 

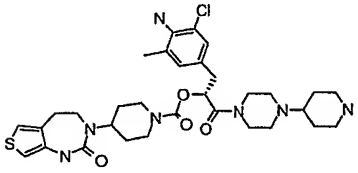
572 

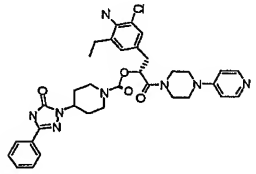
573 

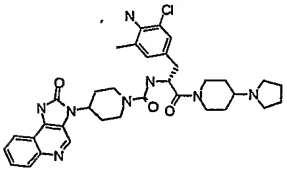
574 

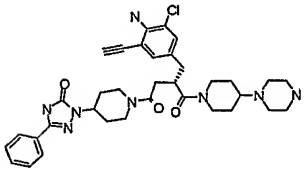
426 

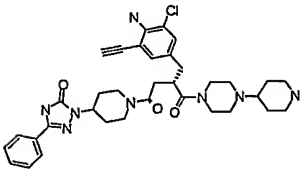
427 

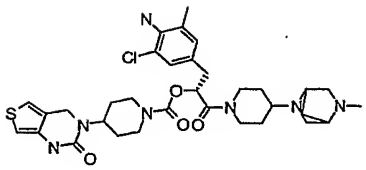
428 

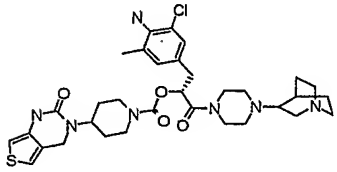
429 

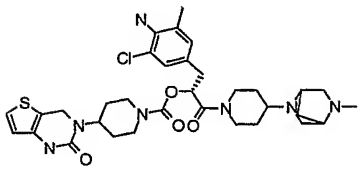
430 

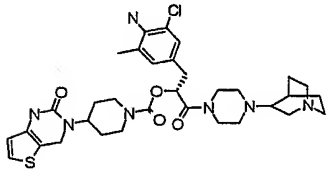
431 

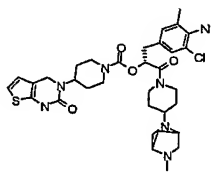
432 

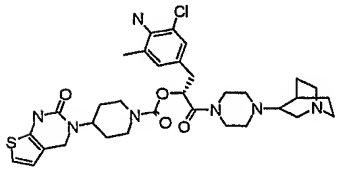
575 

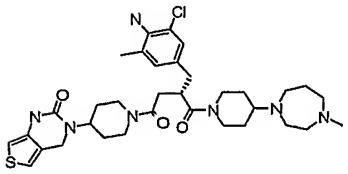
576 

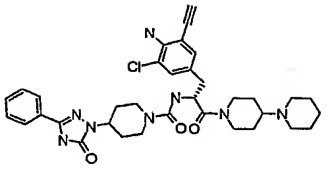
577 

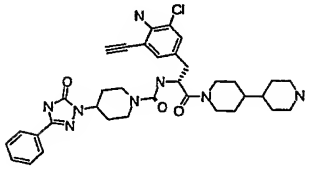
578 

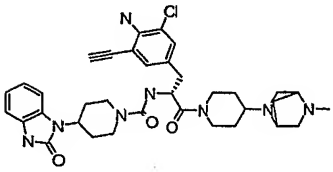
579 

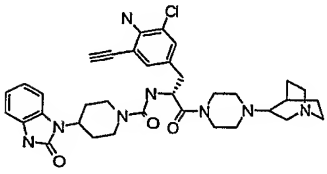
580 

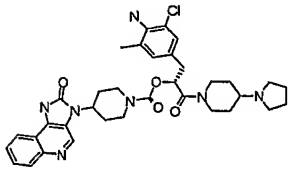
581 

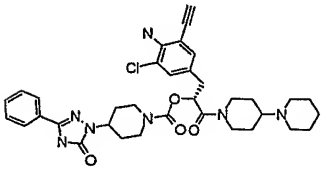
433 

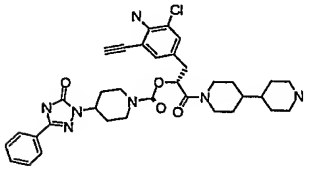
434 

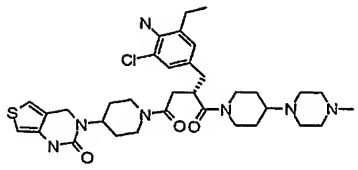
435 

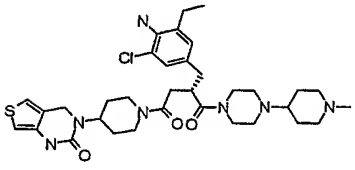
436 

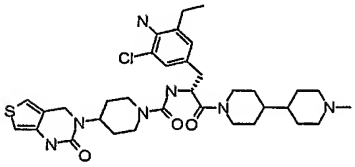
437 

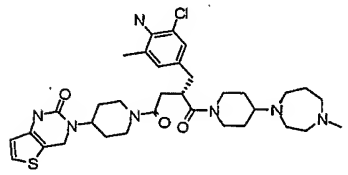
438 

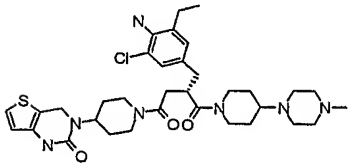
439 

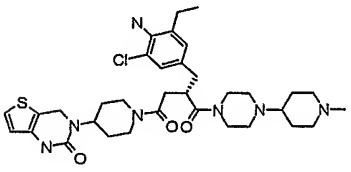
582 

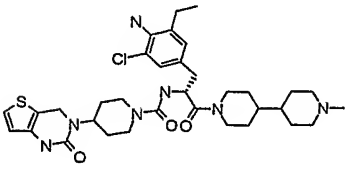
583 

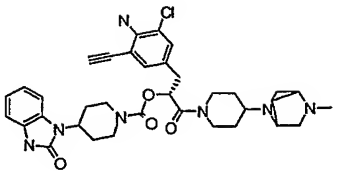
584 

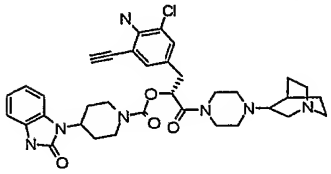
585 

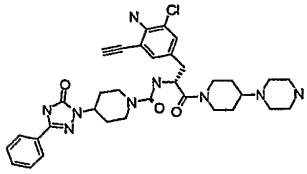
586 

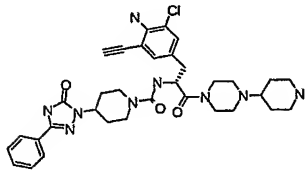
587 

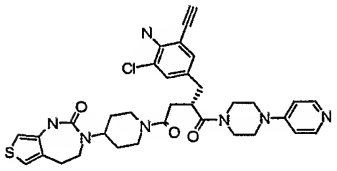
588 

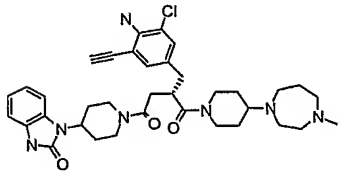
440 

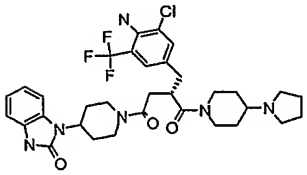
441 

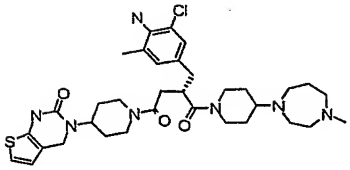
442 

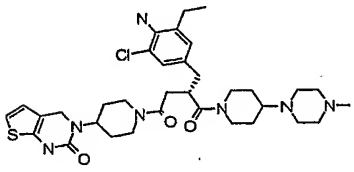
443 

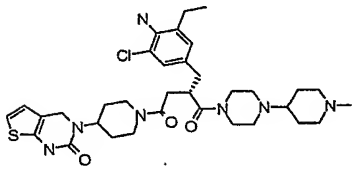
444 

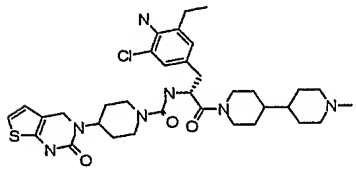
445 

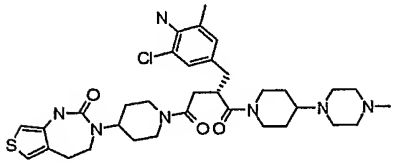
446 

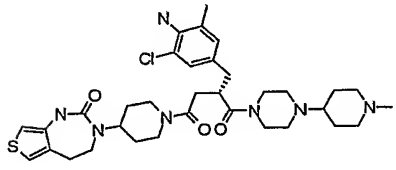
589 

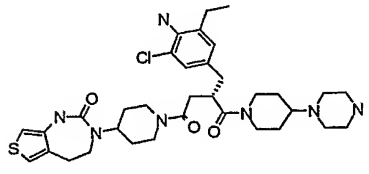
590 

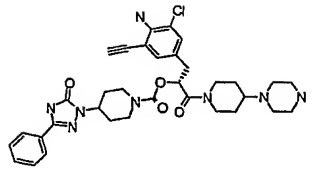
591 

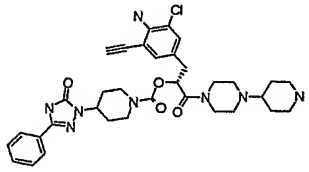
592 

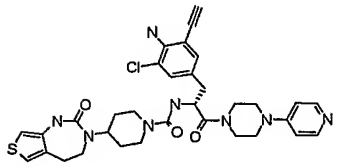
593 

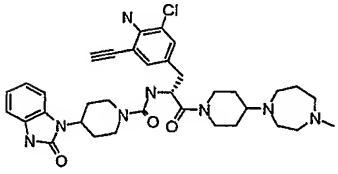
594 

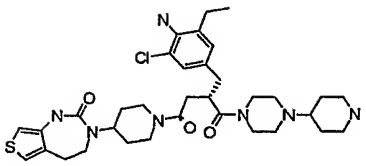
595 

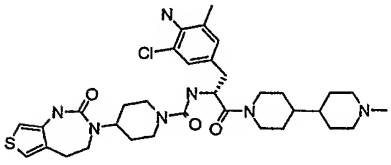
447 

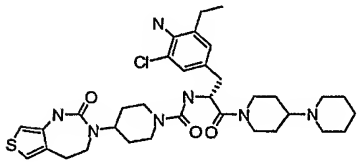
448 

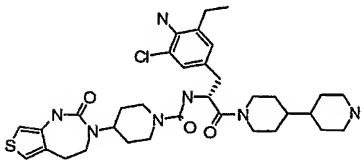
449 

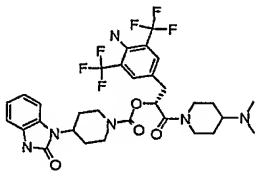
450 

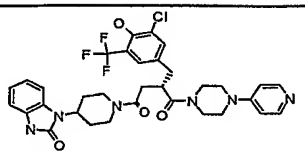
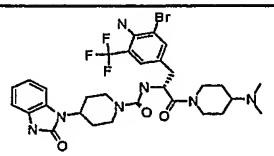
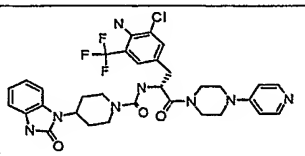
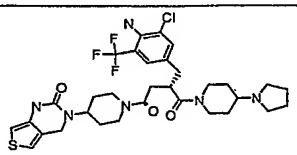
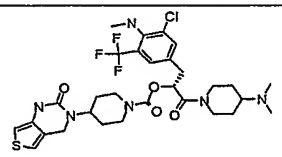
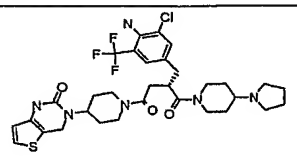
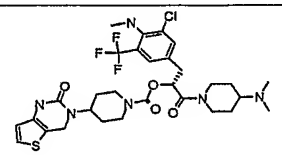
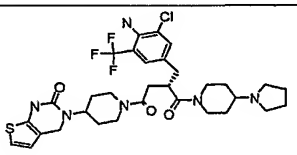
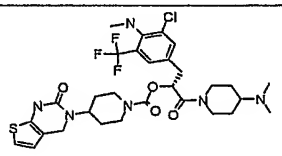
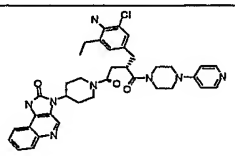
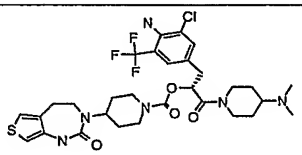
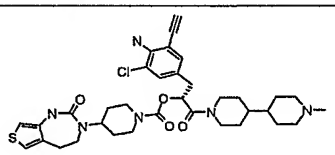
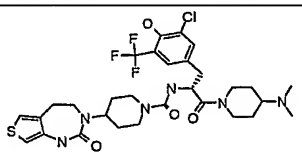
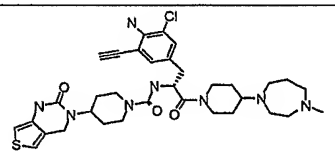
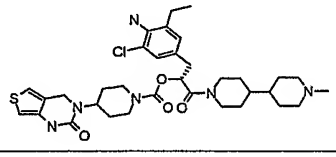
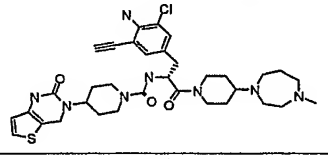
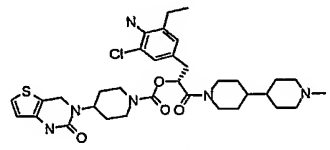
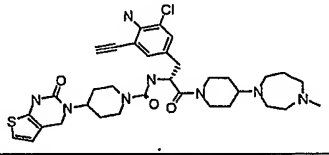
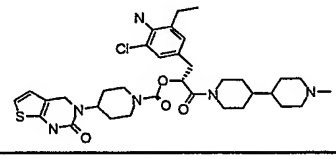
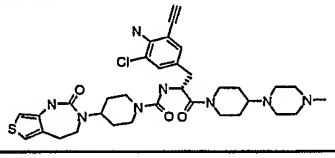
596 

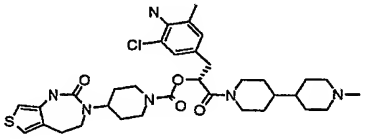
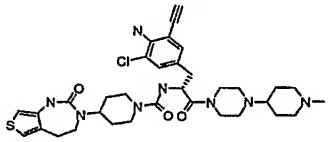
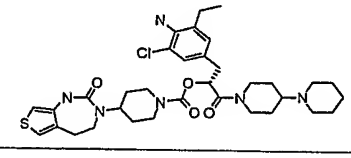
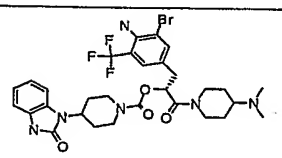
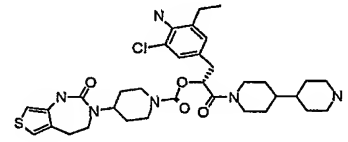
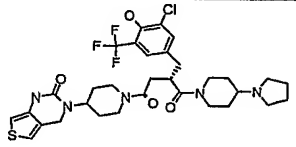
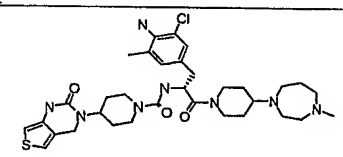
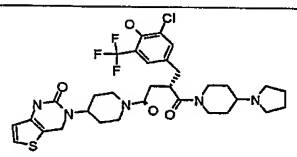
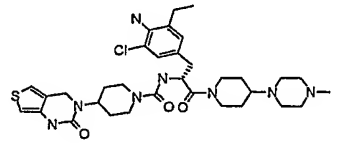
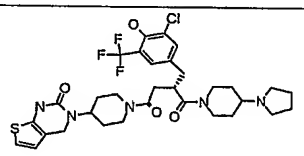
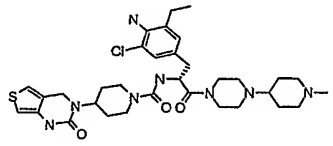
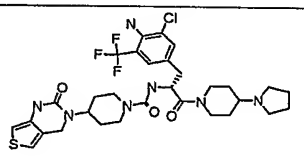
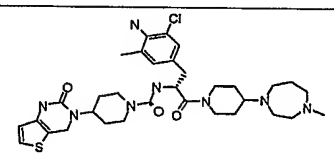
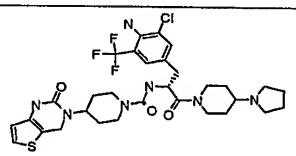
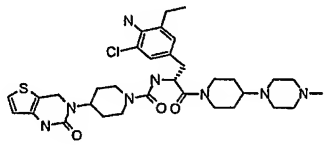
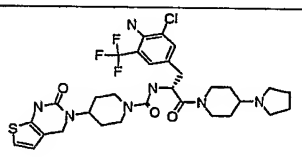
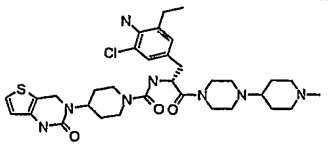
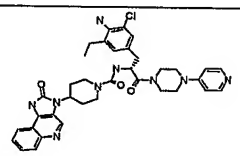
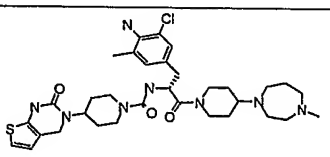
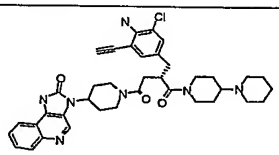
597 

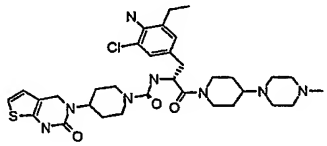
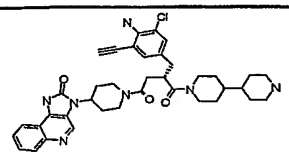
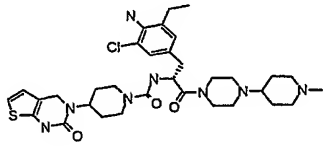
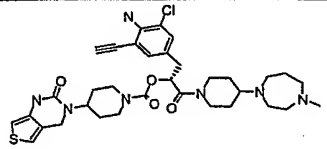
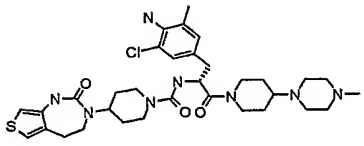
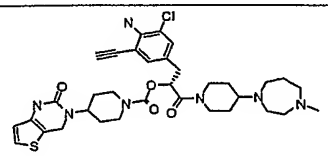
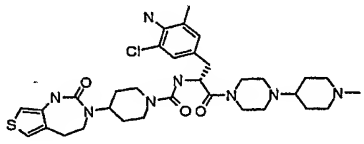
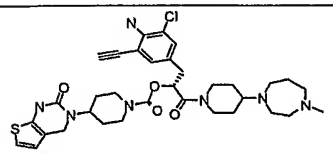
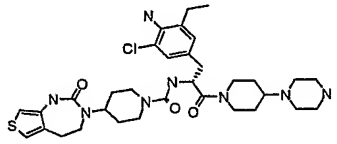
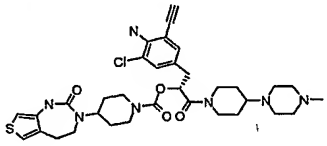
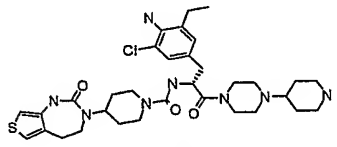
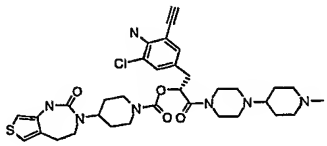
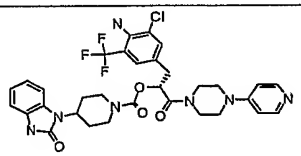
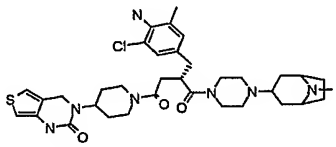
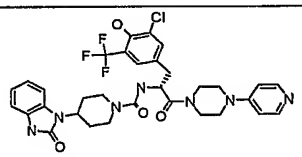
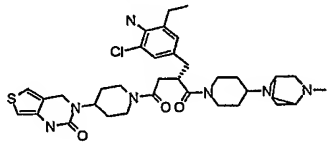
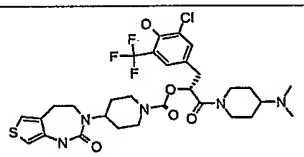
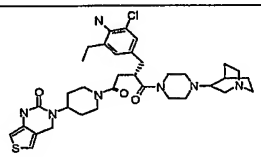
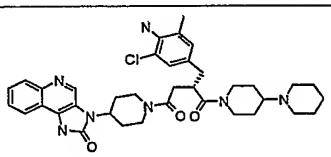
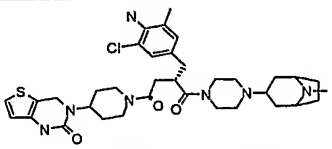
598 

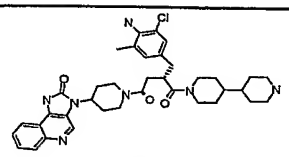
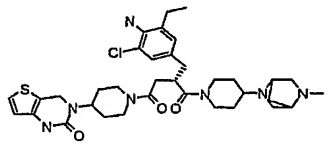
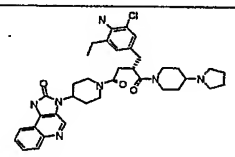
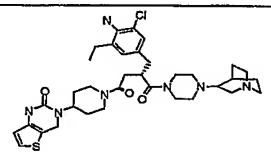
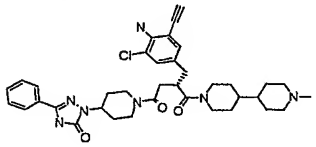
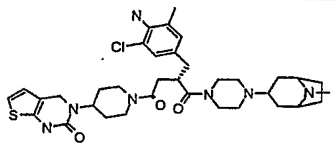
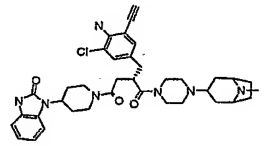
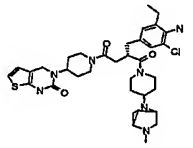
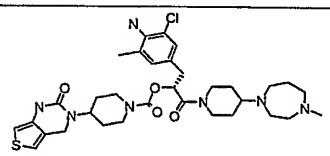
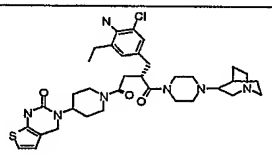
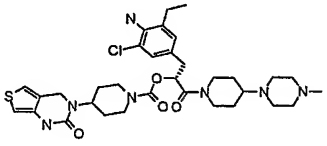
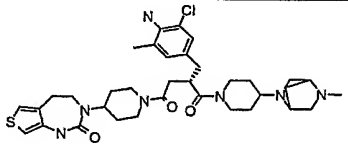
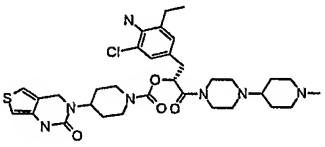
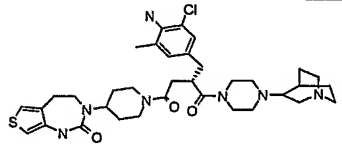
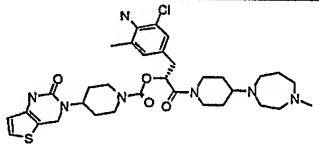
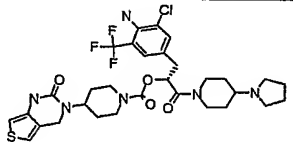
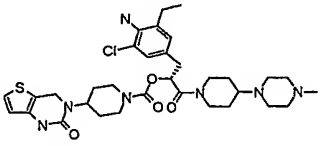
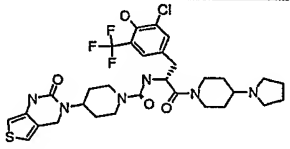
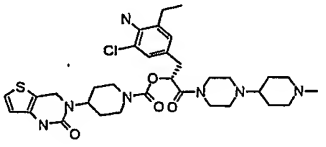
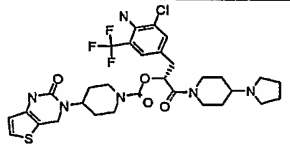
599 

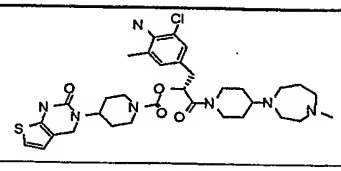
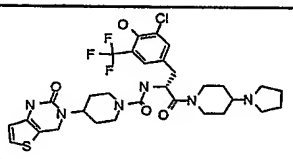
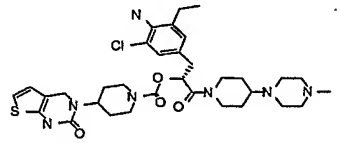
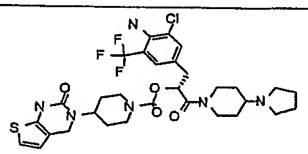
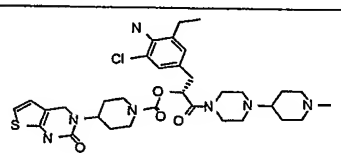
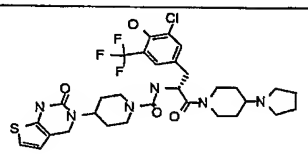
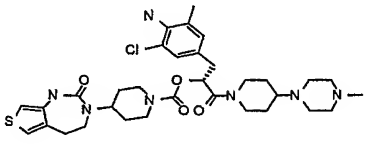
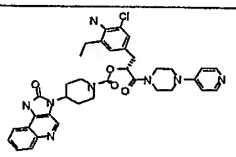
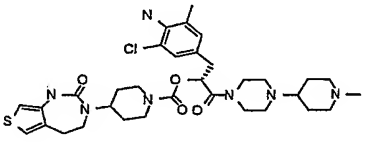
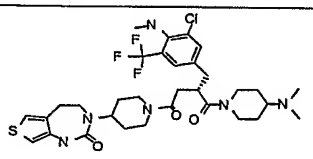
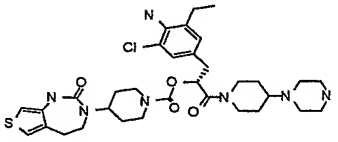
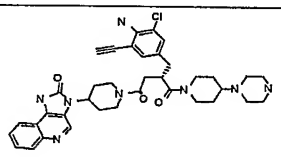
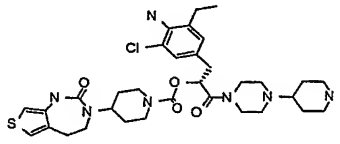
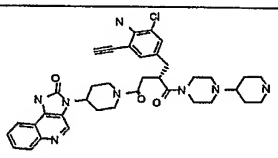
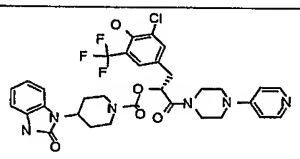
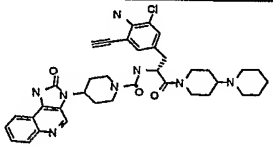
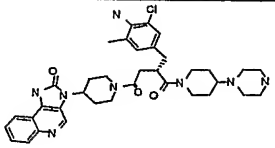
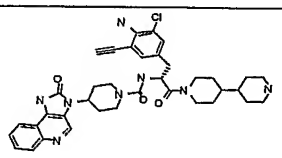
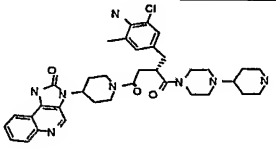
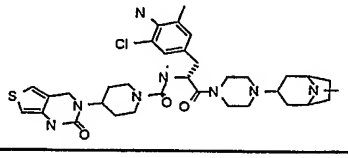
600 

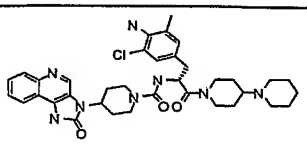
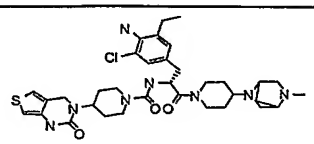
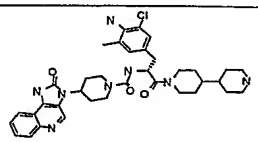
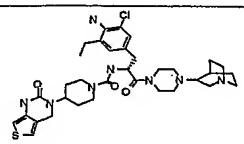
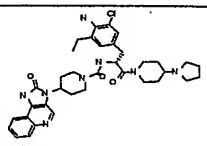
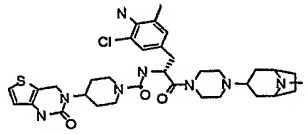
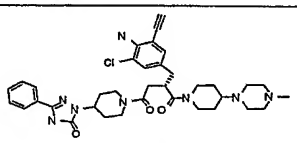
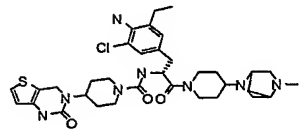
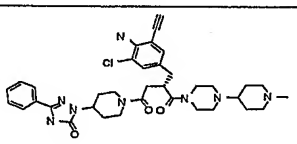
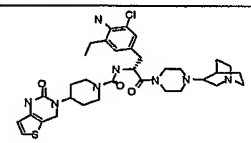
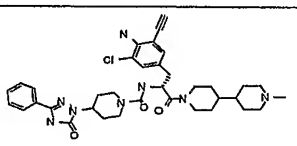
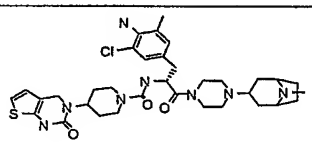
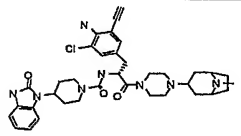
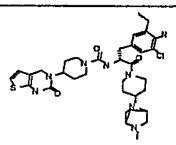
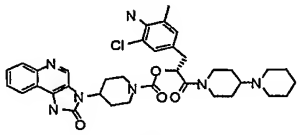
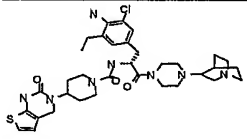
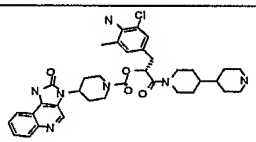
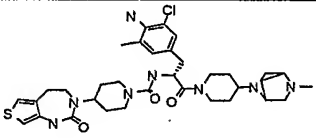
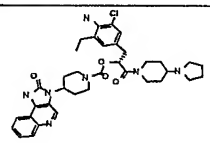
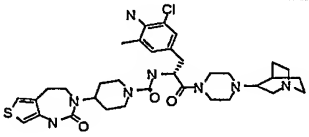
601		751	
602		752	
603		753	
604		754	
605		755	
606		756	
607		757	
608		758	
609		759	
610		760	

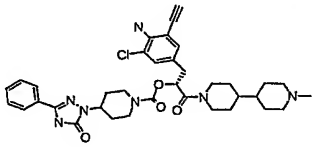
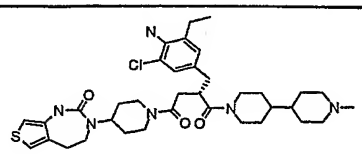
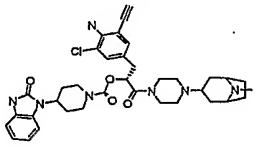
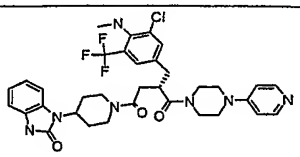
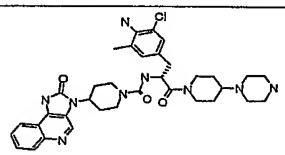
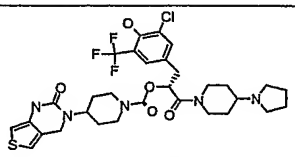
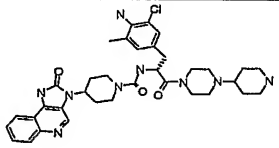
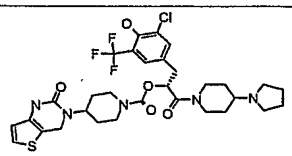
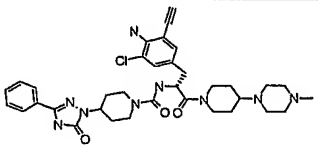
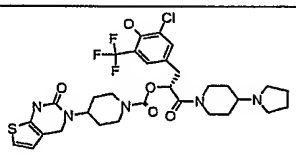
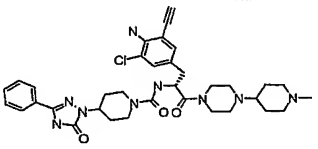
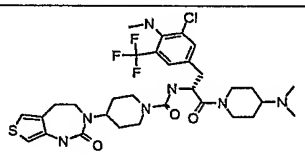
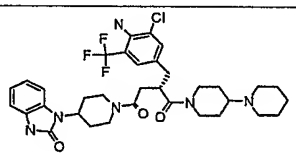
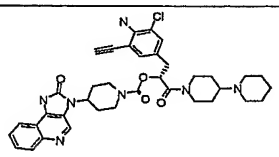
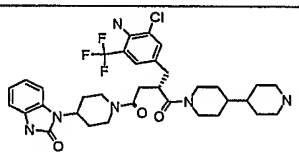
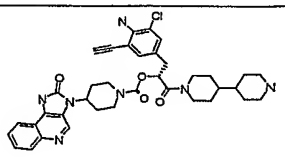
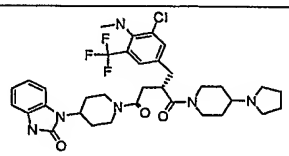
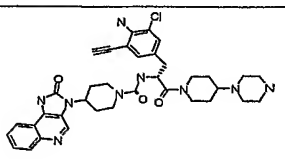
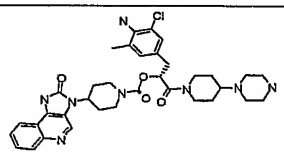
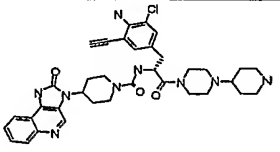
611		761	
612		762	
613		763	
614		764	
615		765	
616		766	
617		767	
618		768	
619		769	
620		770	

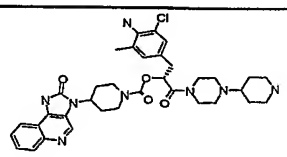
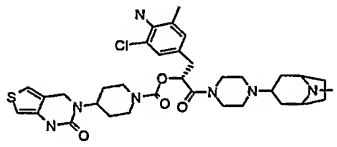
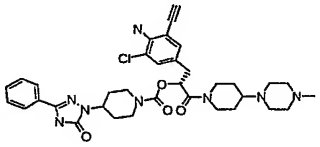
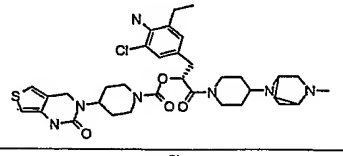
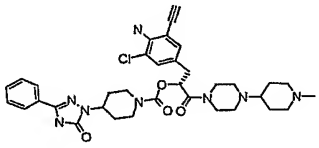
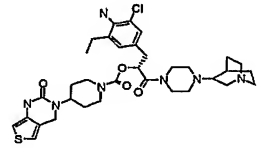
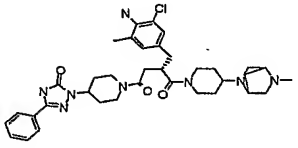
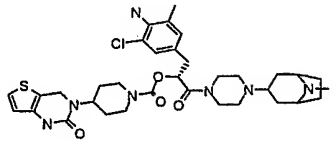
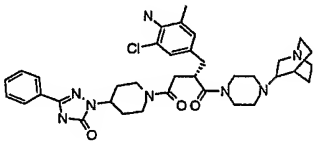
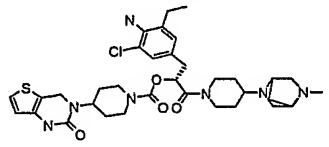
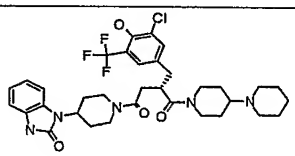
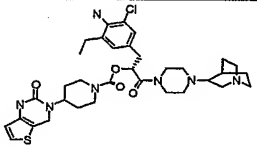
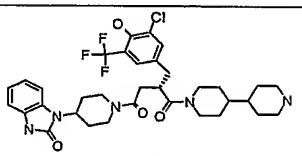
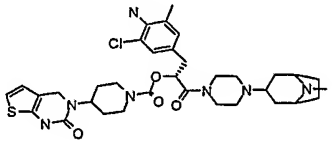
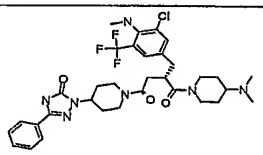
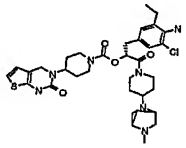
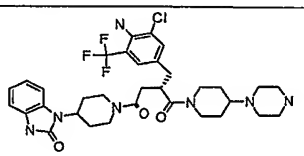
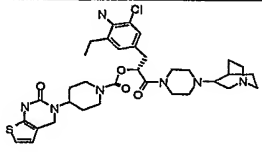
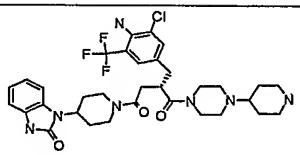
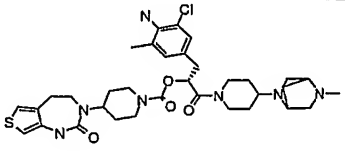
621		771	
622		772	
623		773	
624		774	
625		775	
626		776	
627		777	
628		778	
629		779	
630		780	

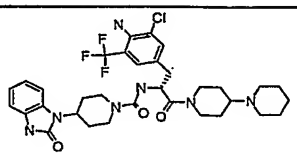
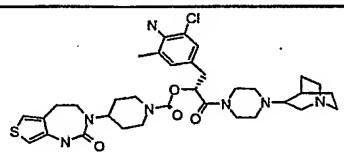
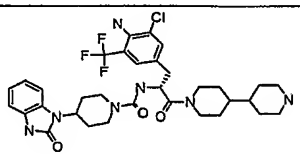
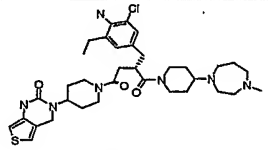
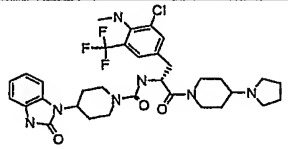
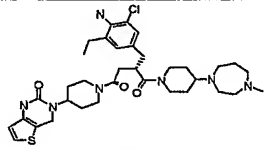
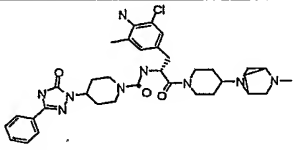
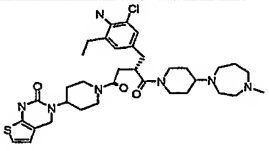
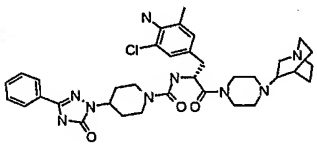
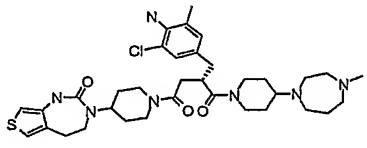
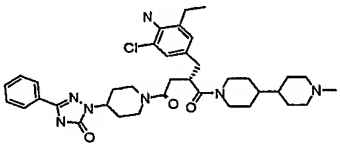
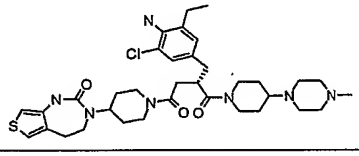
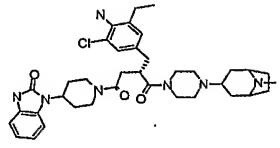
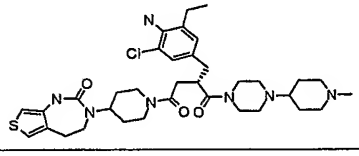
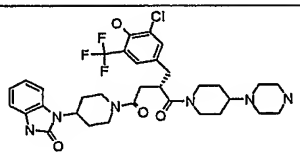
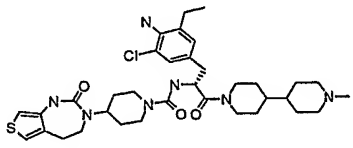
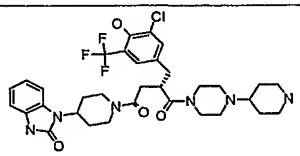
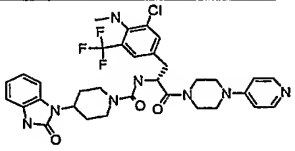
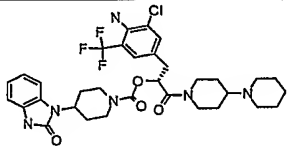
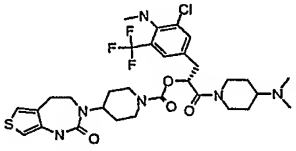
631		781	
632		782	
633		783	
634		784	
635		785	
636		786	
637		787	
638		788	
639		789	
640		790	

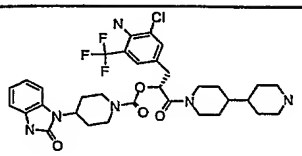
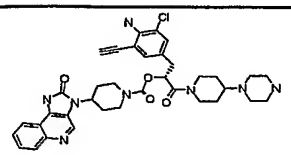
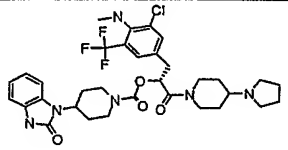
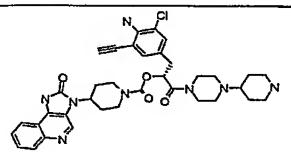
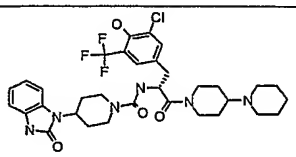
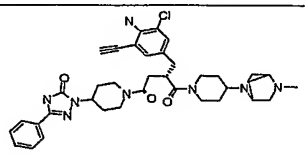
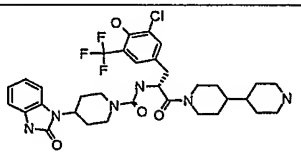
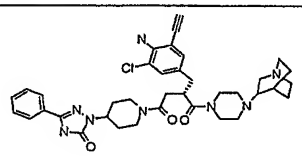
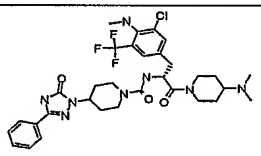
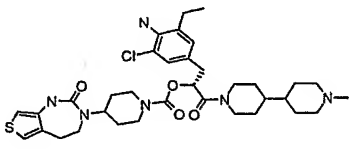
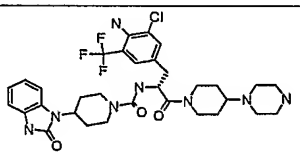
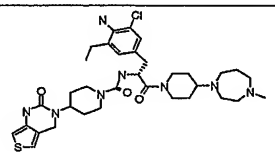
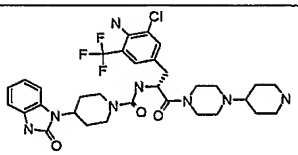
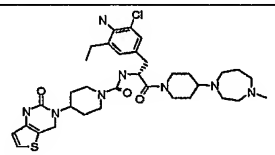
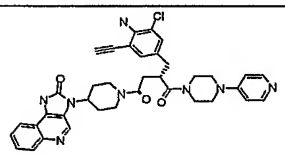
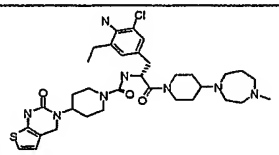
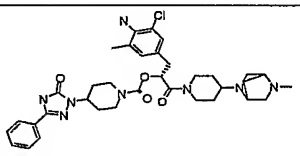
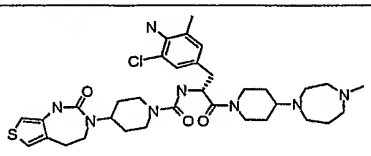
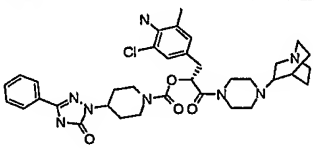
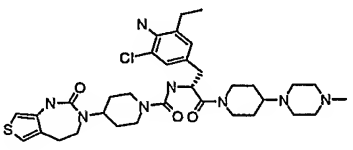
641		791	
642		792	
643		793	
644		794	
645		795	
646		796	
647		797	
648		798	
649		799	
650		800	

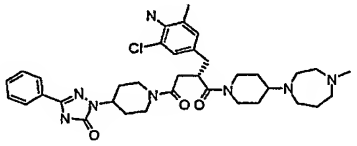
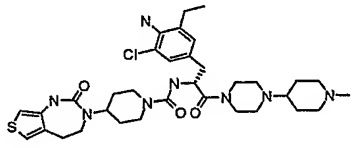
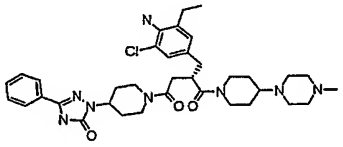
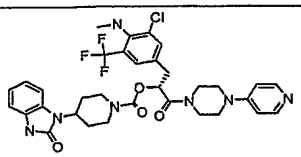
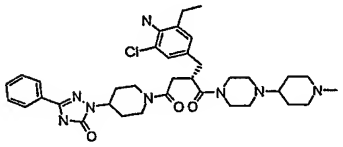
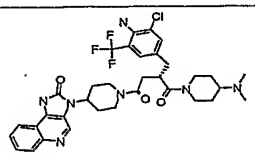
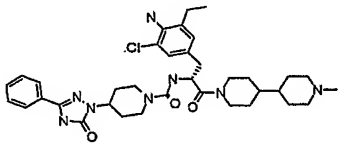
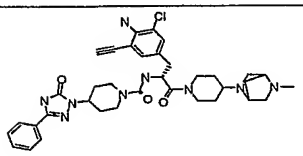
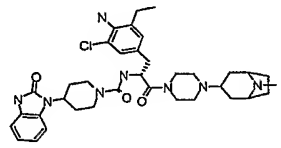
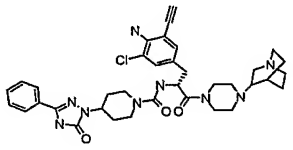
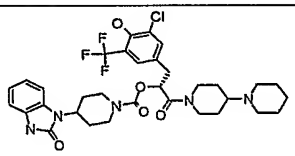
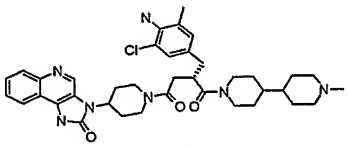
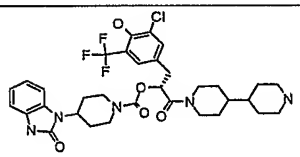
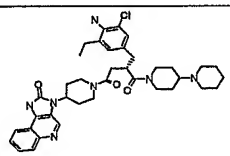
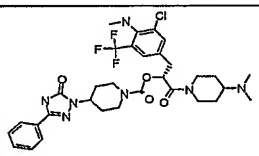
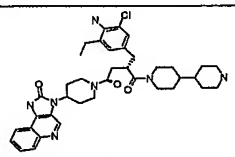
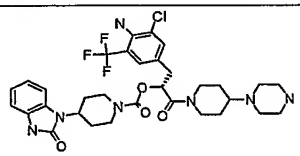
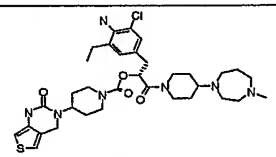
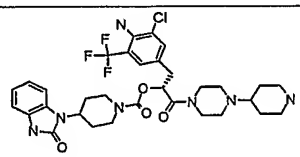
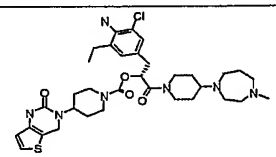
651		801		51
652		802		52
653		803		53
654		804		54
655		805		55
656		806		56
657		807		57
658		808		58
659		809		59
660		810		60

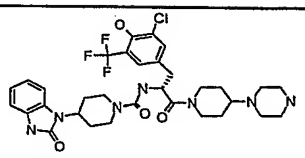
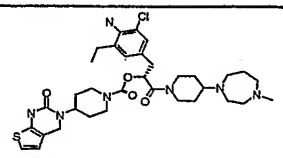
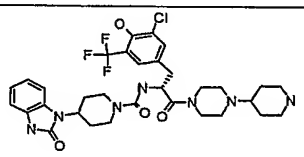
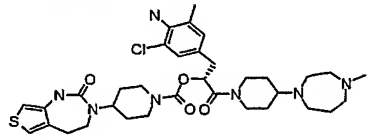
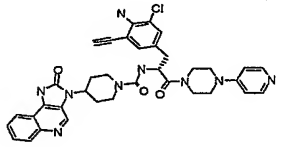
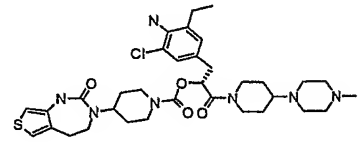
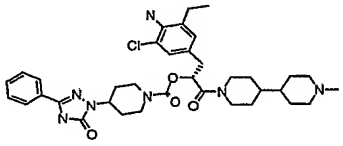
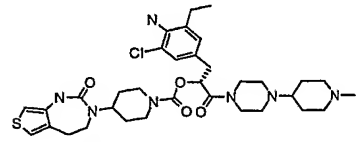
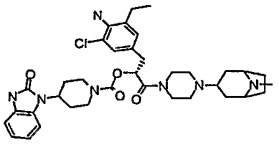
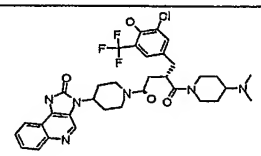
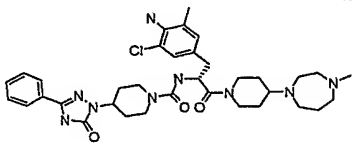
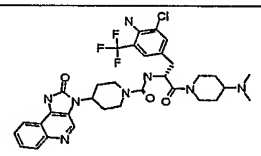
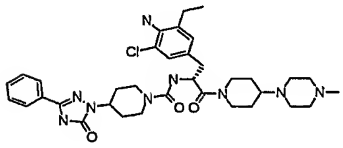
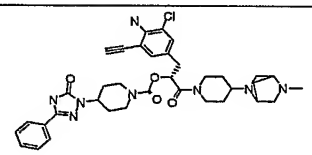
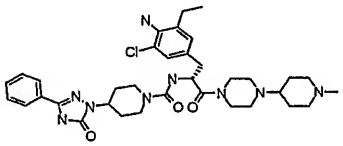
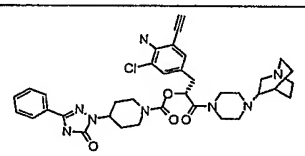
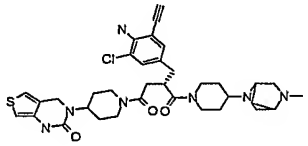
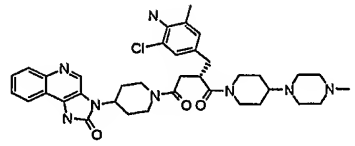
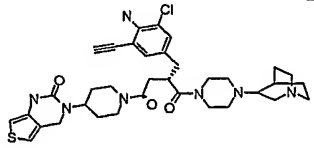
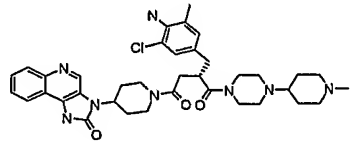
661		811	
662		812	
663		813	
664		814	
665		815	
666		816	
667		817	
668		818	
669		819	
670		820	

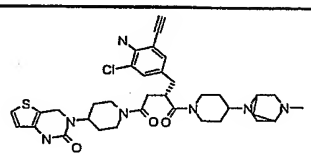
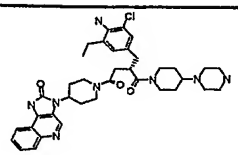
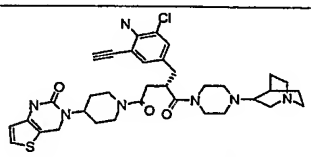
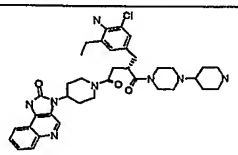
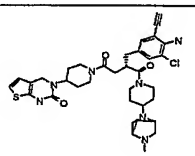
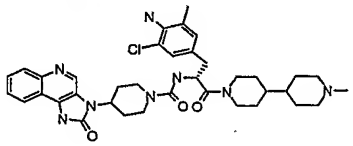
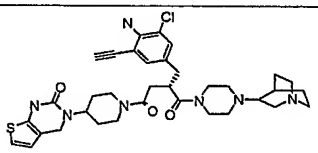
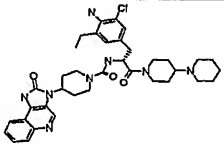
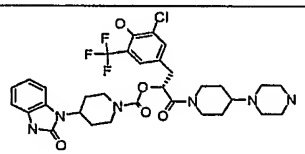
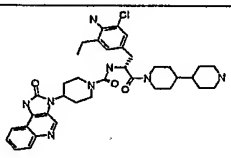
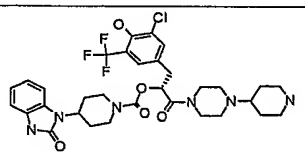
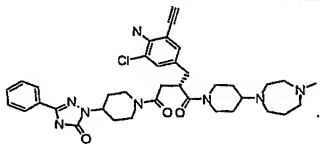
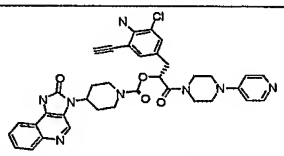
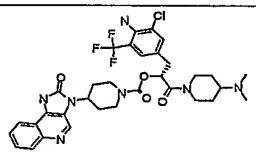
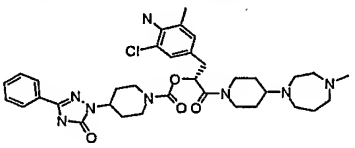
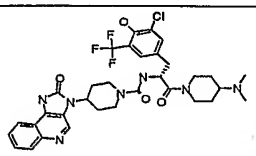
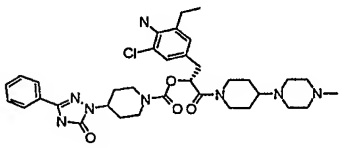
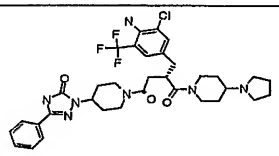
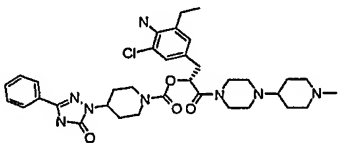
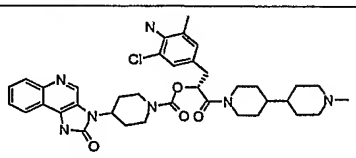
671		821	
672		822	
673		823	
674		824	
675		825	
676		826	
677		827	
678		828	
679		829	
680		830	

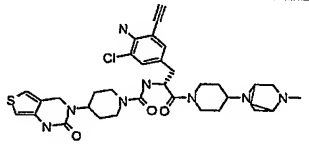
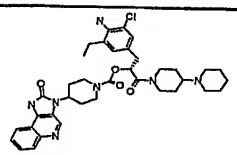
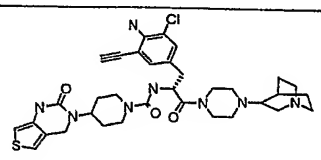
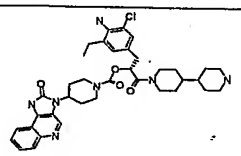
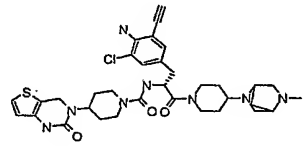
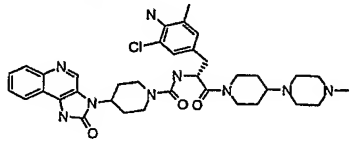
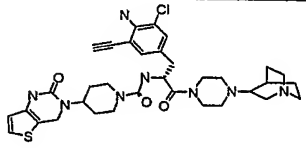
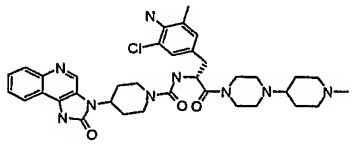
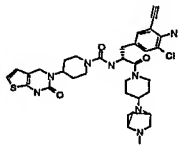
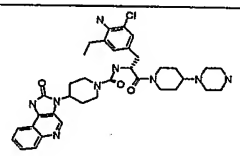
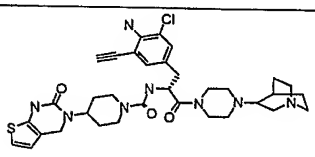
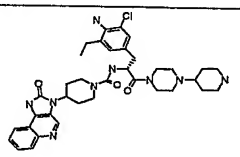
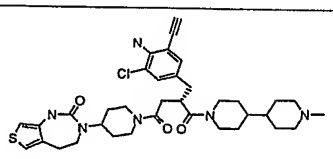
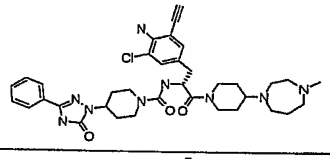
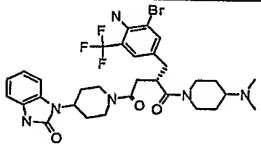
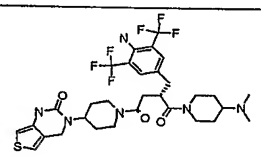
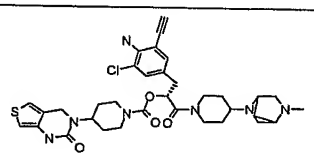
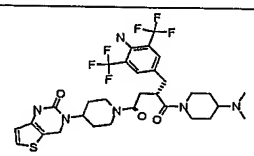
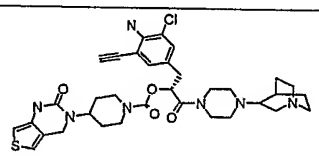
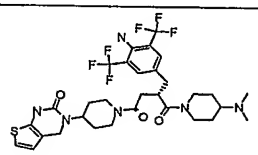
681		831	
682		832	
683		833	
684		834	
685		835	
686		836	
687		837	
688		838	
689		839	
690		840	

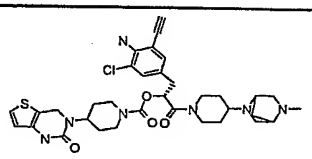
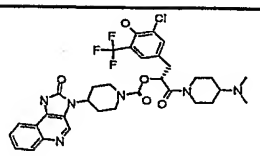
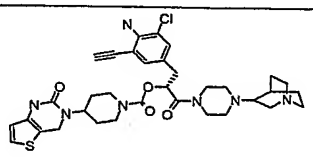
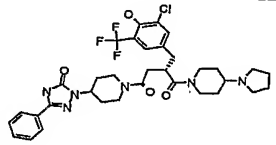
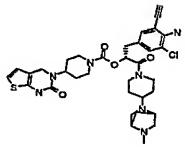
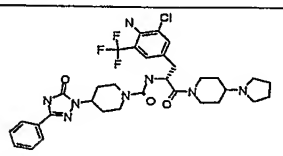
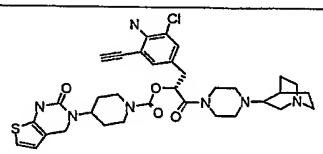
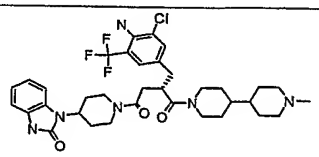
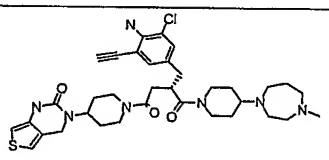
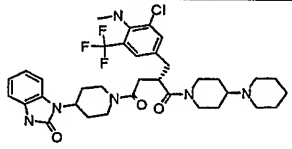
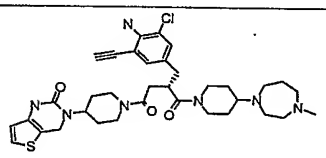
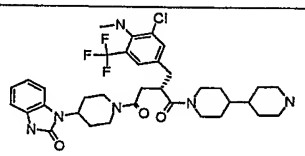
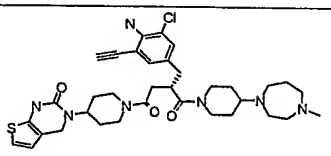
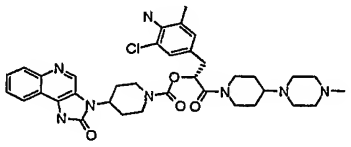
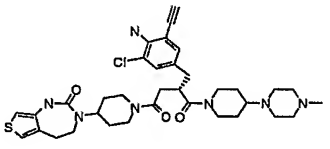
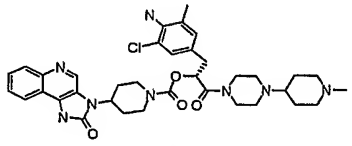
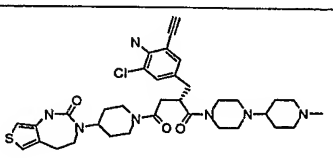
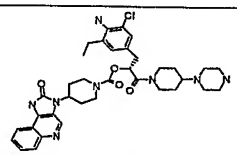
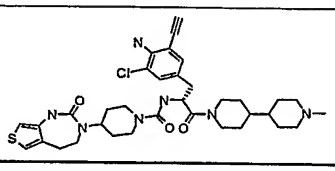
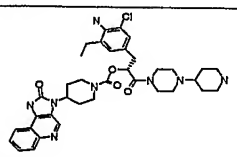
691		841	
692		842	
693		843	
694		844	
695		845	
696		846	
697		847	
698		848	
699		849	
700		850	

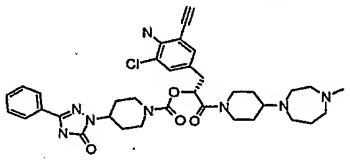
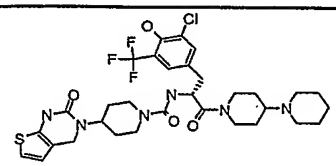
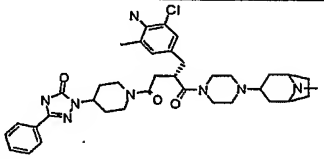
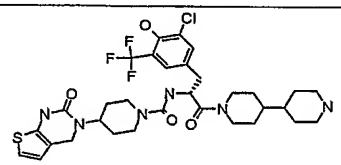
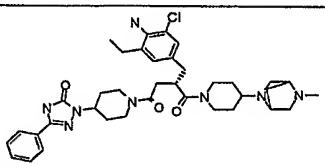
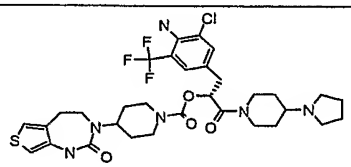
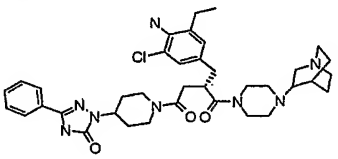
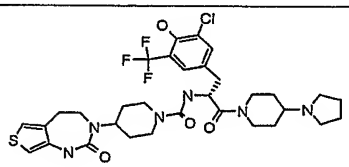
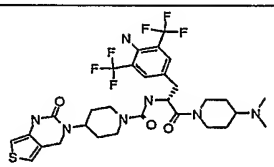
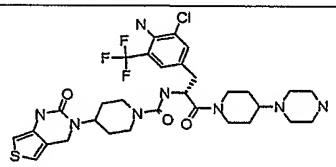
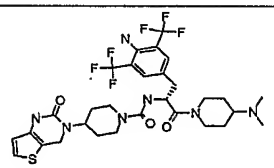
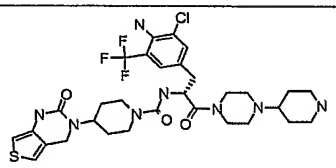
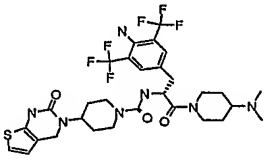
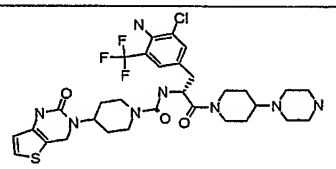
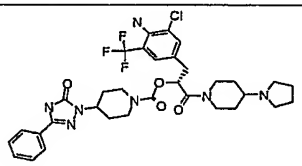
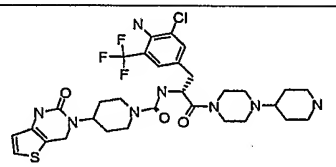
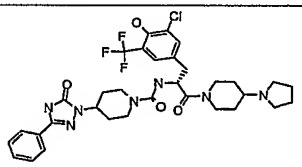
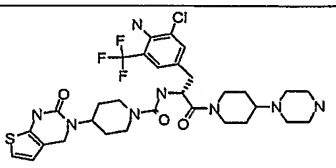
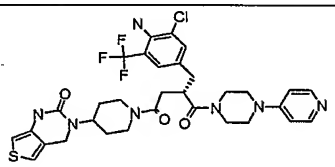
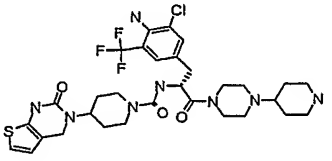
701		851	
702		852	
703		853	
704		854	
705		855	
706		856	
707		857	
708		858	
709		859	
710		860	

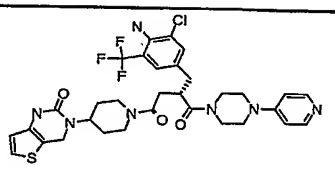
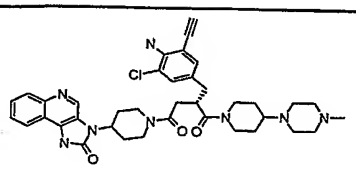
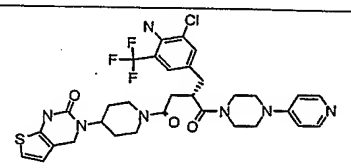
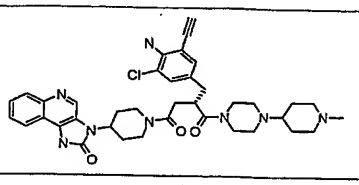
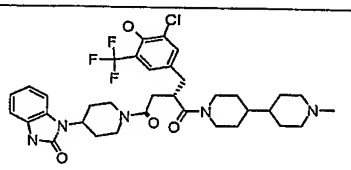
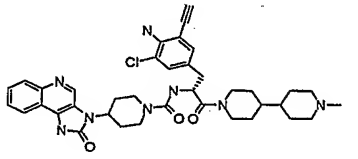
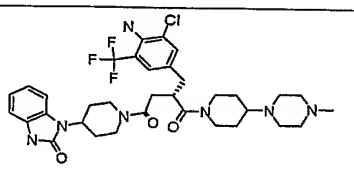
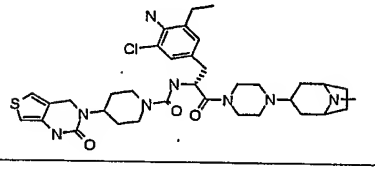
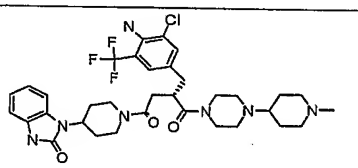
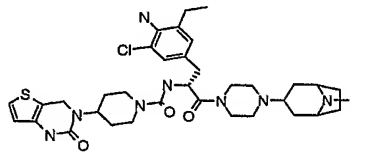
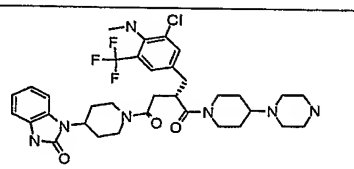
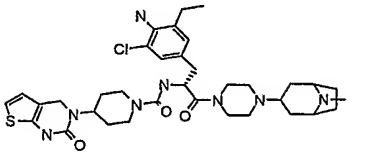
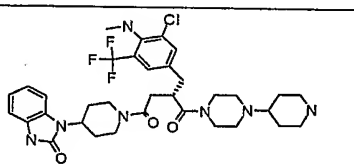
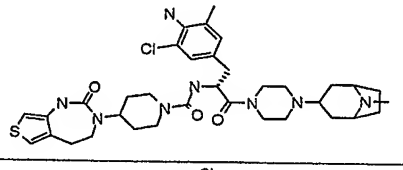
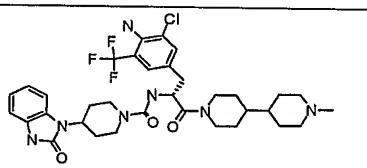
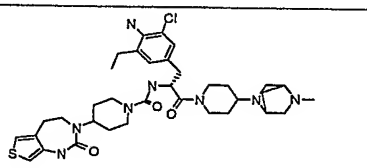
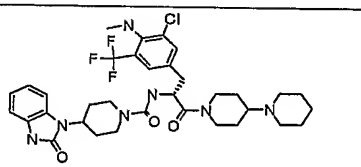
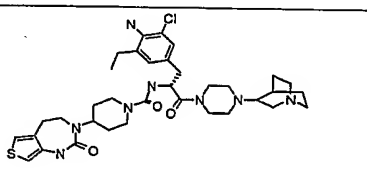
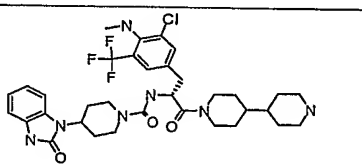
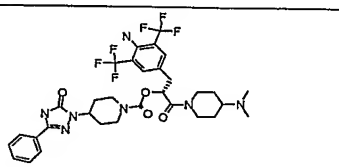
711		861	
712		862	
713		863	
714		864	
715		865	
716		866	
717		867	
718		868	
719		869	
720		870	

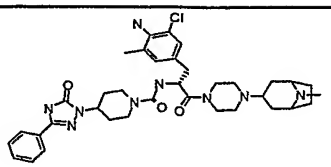
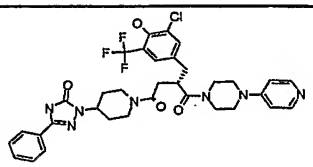
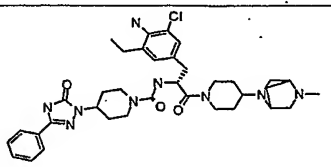
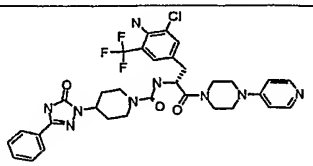
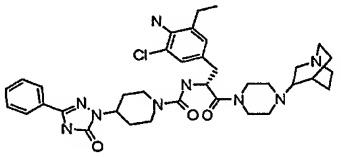
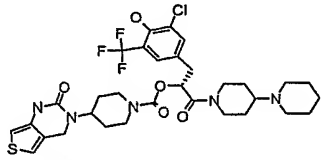
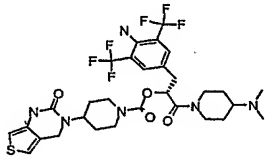
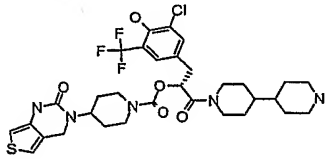
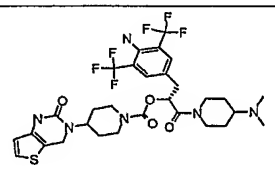
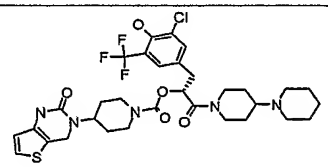
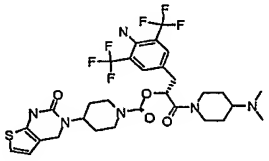
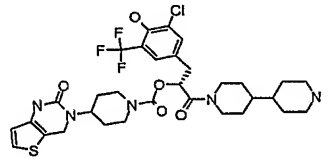
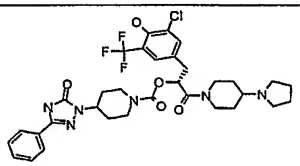
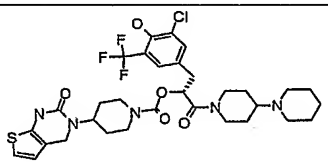
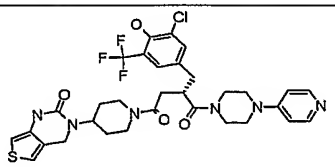
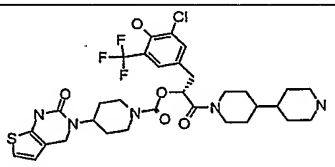
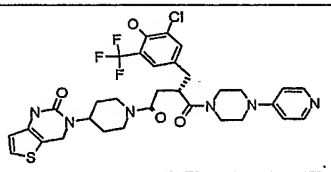
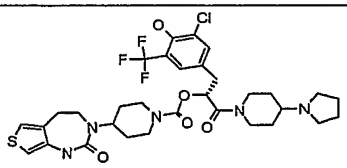
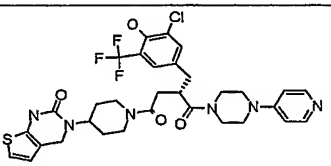
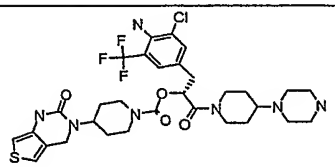
721		871	
722		872	
723		873	
724		874	
725		875	
726		876	
727		877	
728		878	
729		879	
730		880	

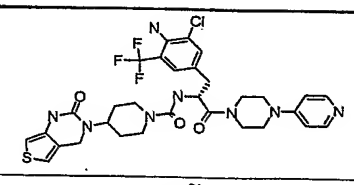
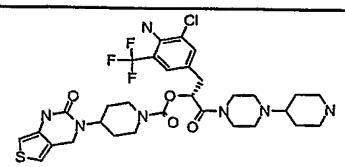
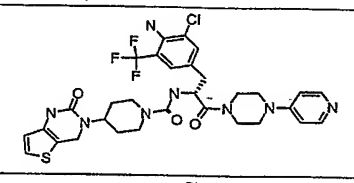
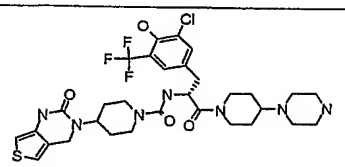
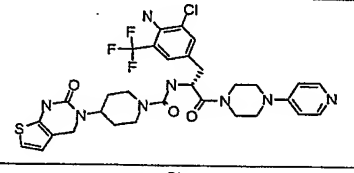
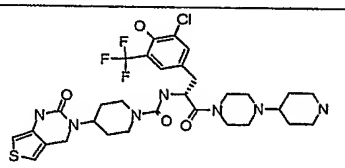
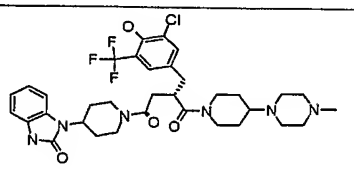
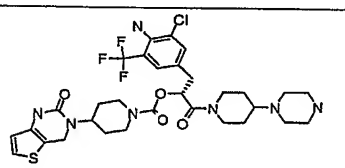
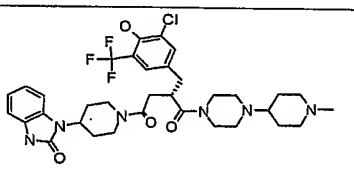
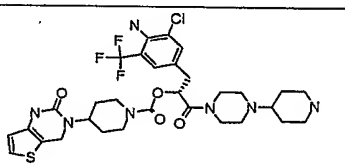
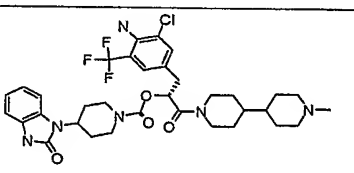
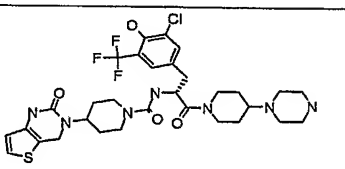
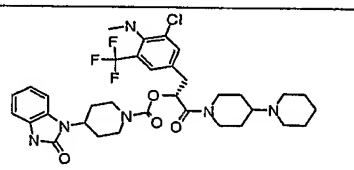
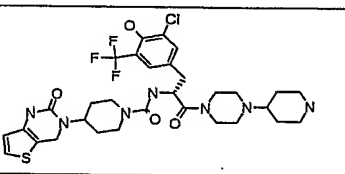
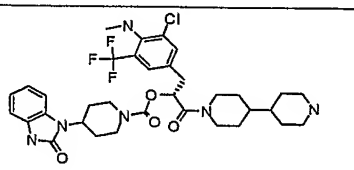
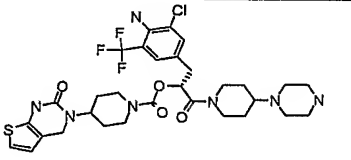
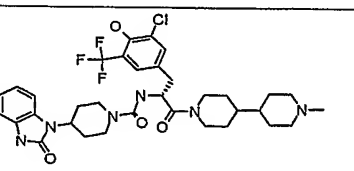
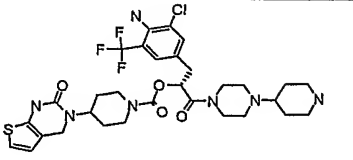
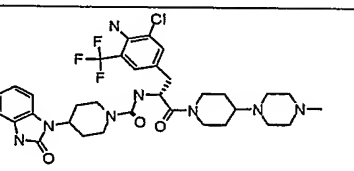
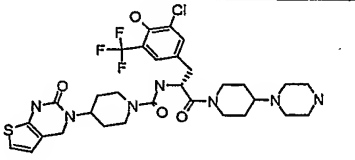
731		881	
732		882	
733		883	
734		884	
735		885	
736		886	
737		887	
738		888	
739		889	
740		890	

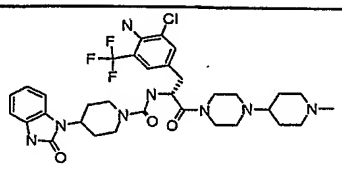
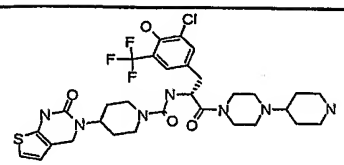
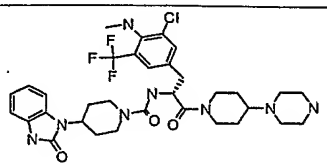
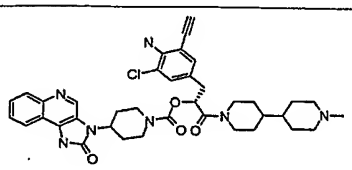
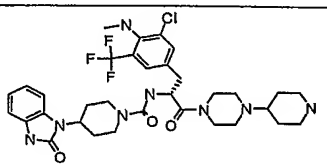
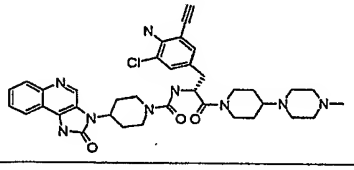
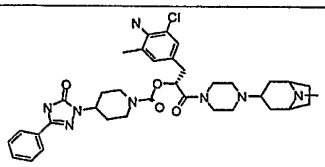
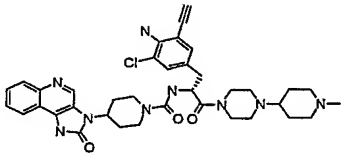
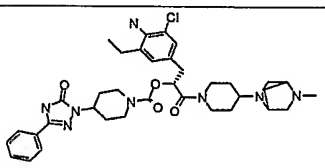
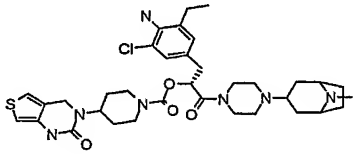
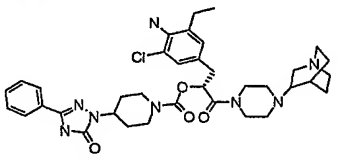
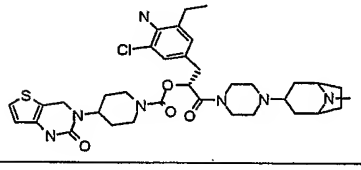
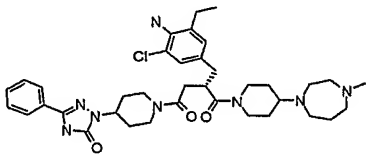
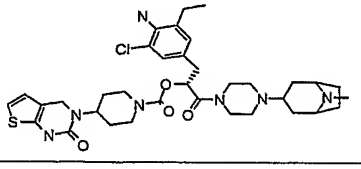
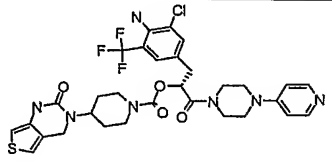
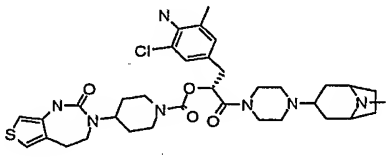
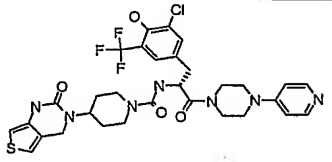
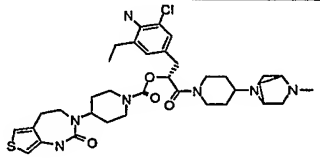
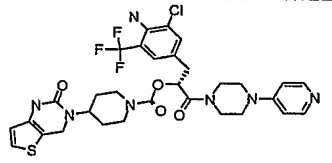
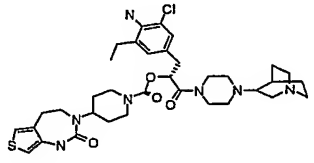
741		891	
742		892	
743		893	
744		894	
745		895	
746		896	
747		897	
748		898	
749		899	
750		900	

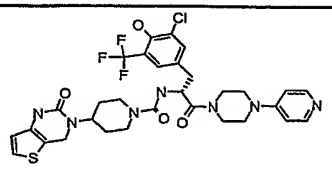
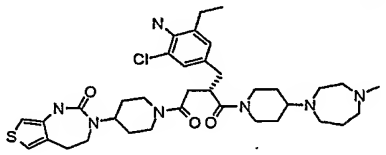
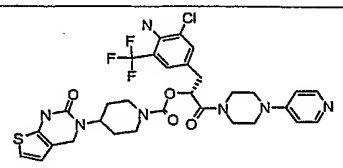
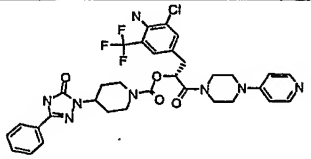
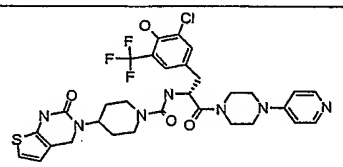
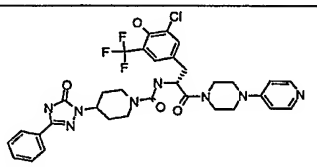
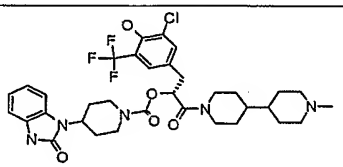
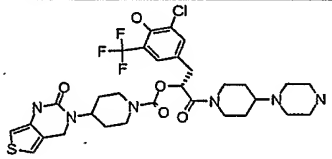
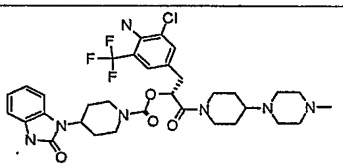
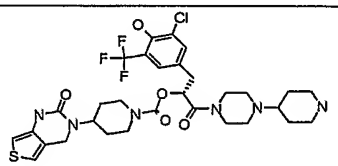
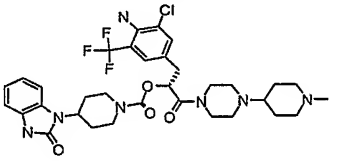
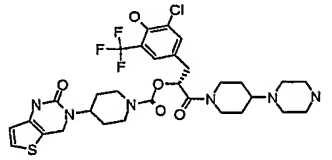
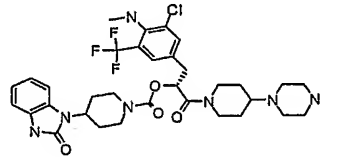
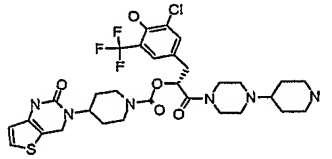
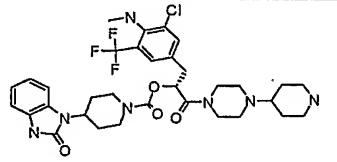
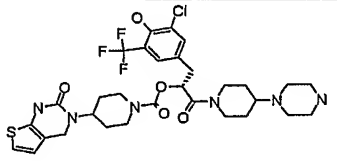
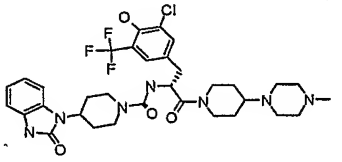
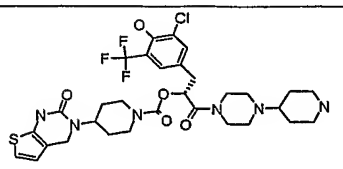
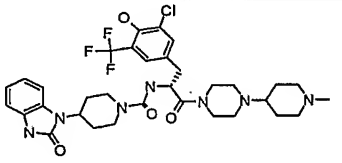
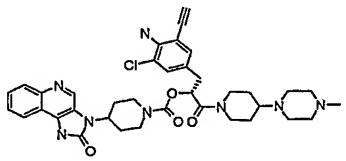
901		1051	
902		1052	
903		1053	
904		1054	
905		1055	
906		1056	
907		1057	
908		1058	
909		1059	
910		1060	

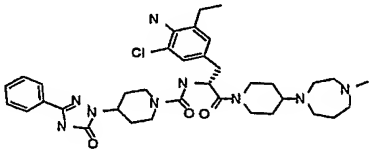
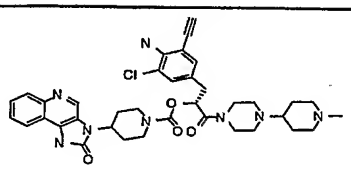
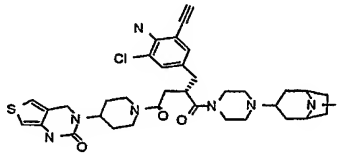
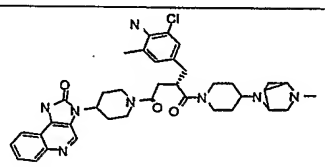
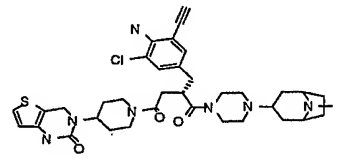
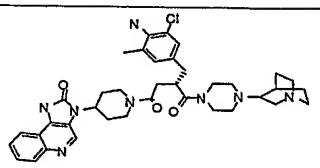
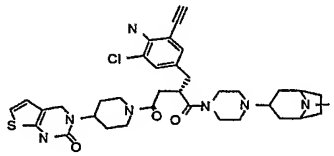
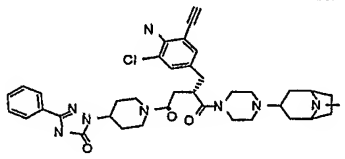
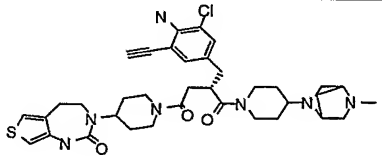
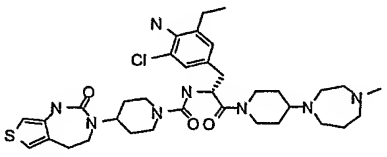
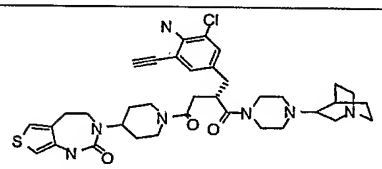
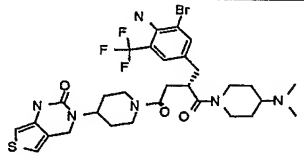
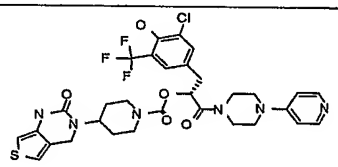
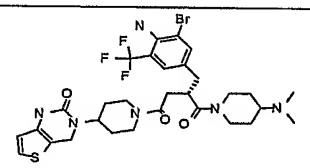
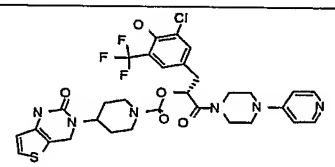
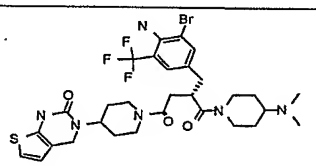
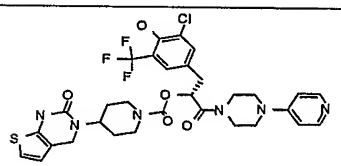
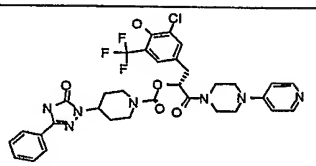
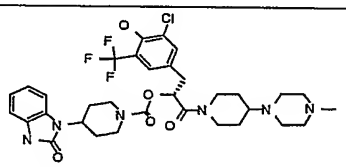
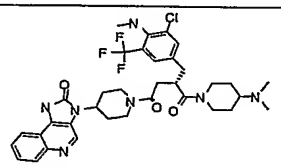
911		1061	
912		1062	
913		1063	
914		1064	
915		1065	
916		1066	
917		1067	
918		1068	
919		1069	
920		1070	

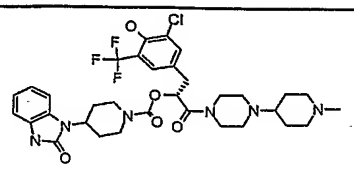
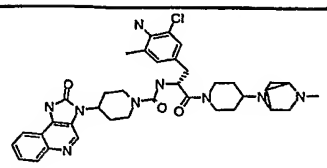
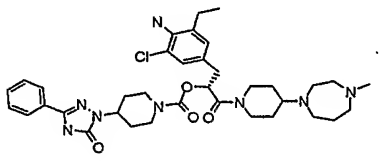
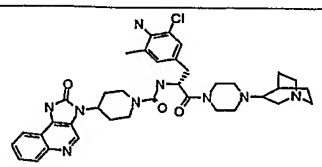
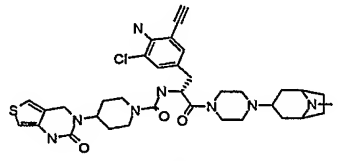
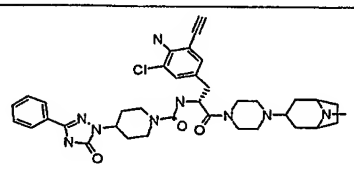
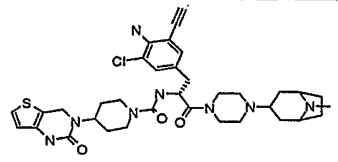
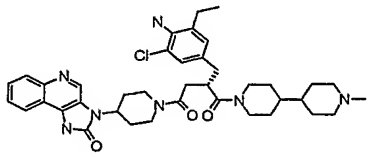
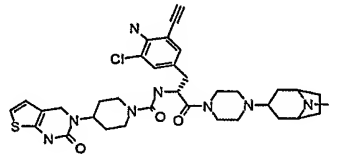
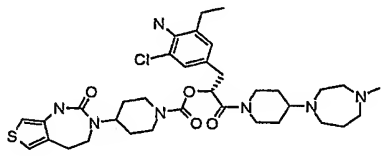
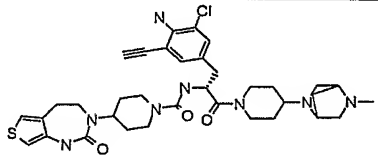
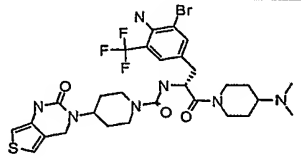
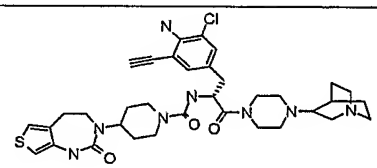
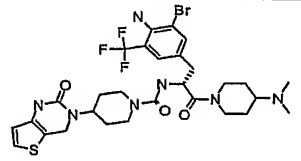
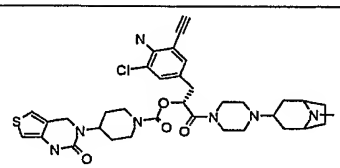
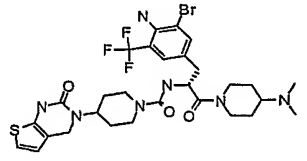
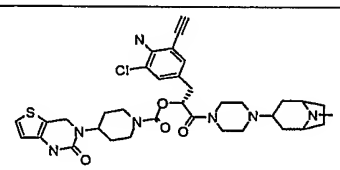
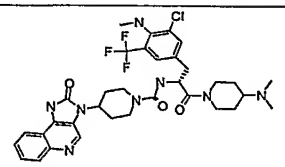
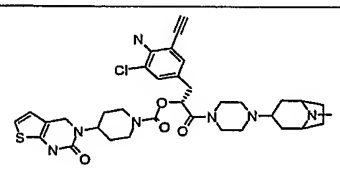
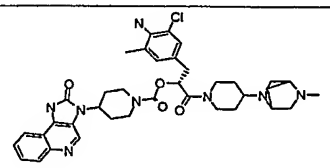
921		1071	
922		1072	
923		1073	
924		1074	
925		1075	
926		1076	
927		1077	
928		1078	
929		1079	
930		1080	

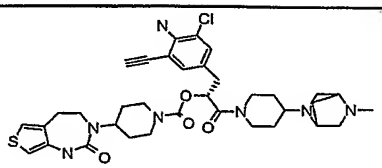
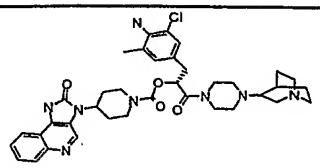
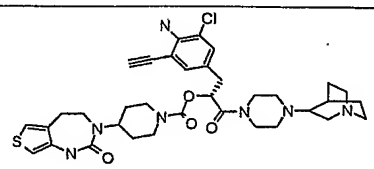
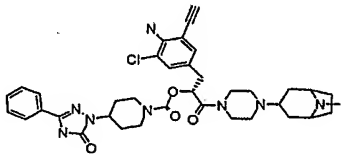
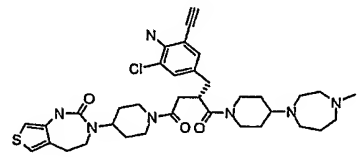
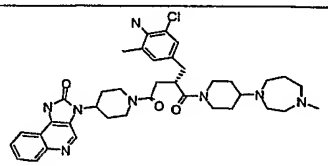
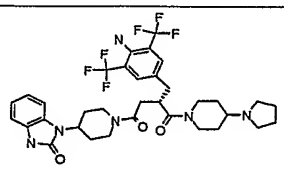
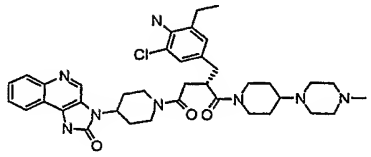
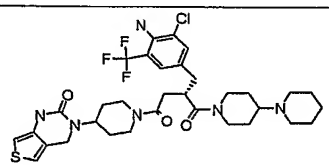
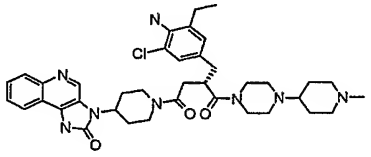
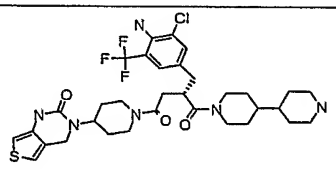
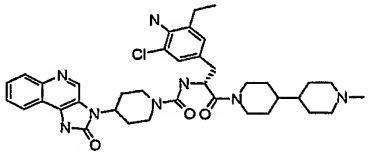
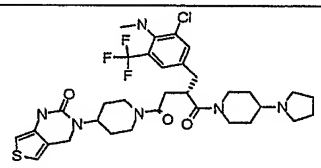
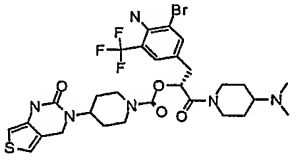
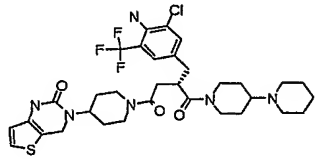
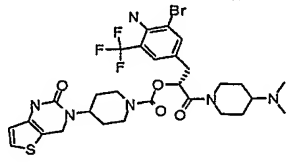
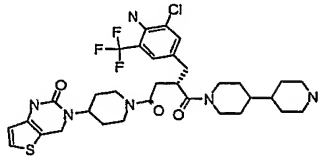
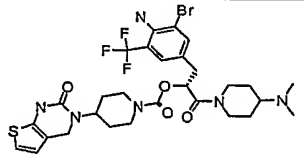
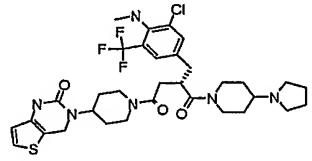
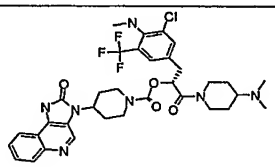
931		1081	
932		1082	
933		1083	
934		1084	
935		1085	
936		1086	
937		1087	
938		1088	
939		1089	
940		1090	

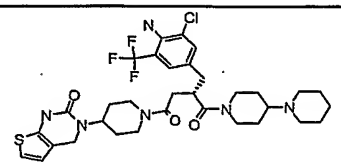
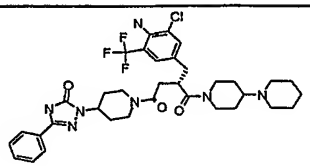
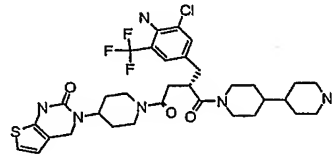
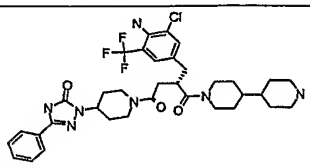
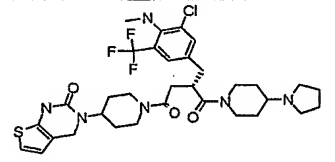
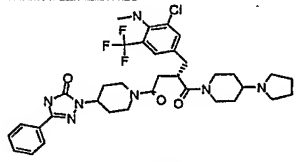
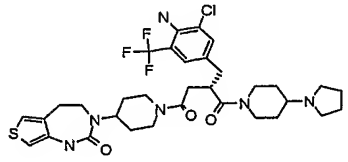
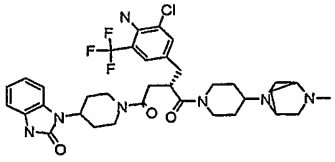
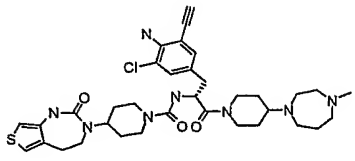
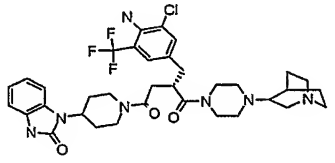
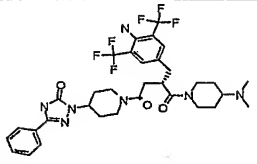
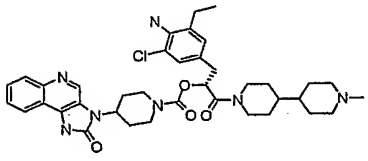
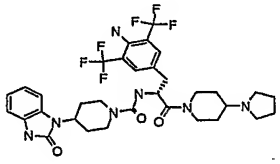
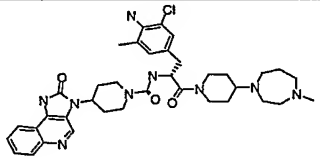
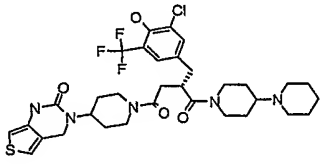
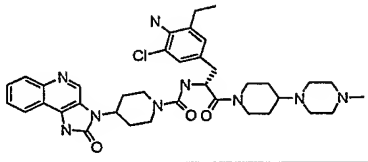
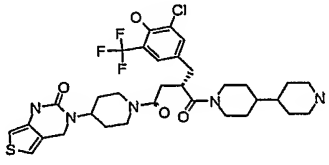
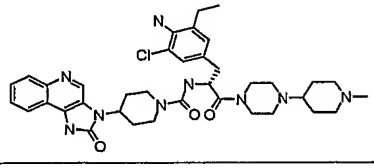
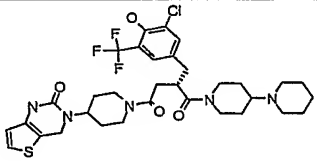
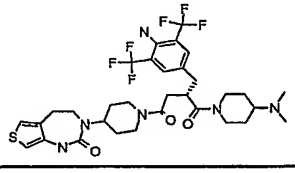
941		1091	
942		1092	
943		1093	
944		1094	
945		1095	
946		1096	
947		1097	
948		1098	
949		1099	
950		1100	

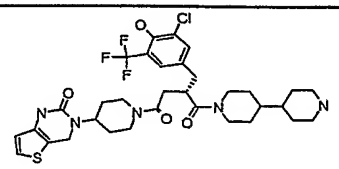
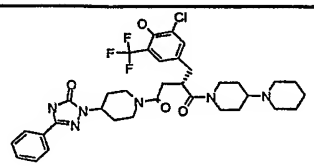
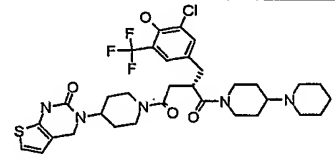
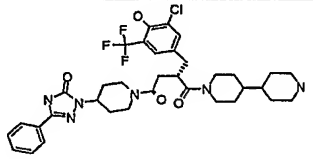
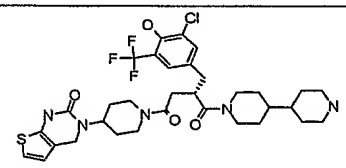
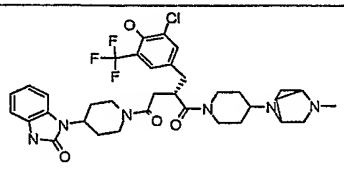
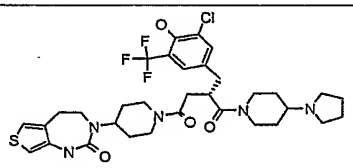
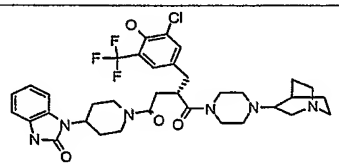
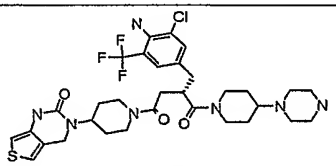
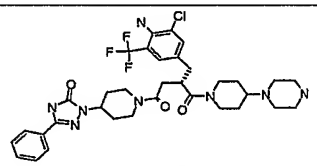
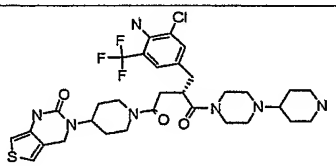
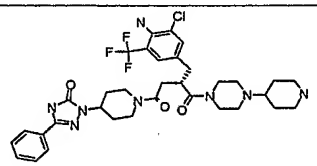
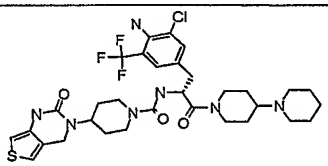
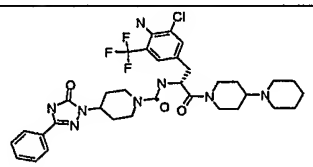
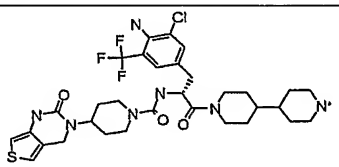
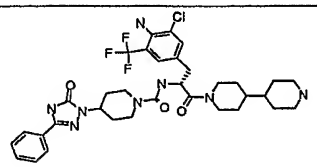
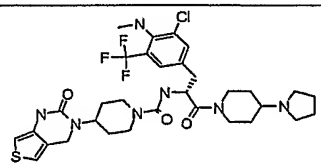
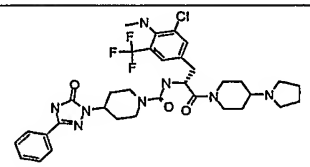
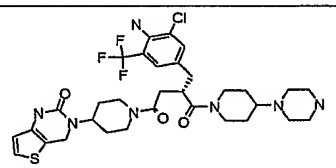
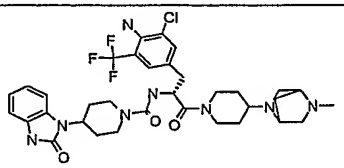
951		1101	
952		1102	
953		1103	
954		1104	
955		1105	
956		1106	
957		1107	
958		1108	
959		1109	
960		1110	

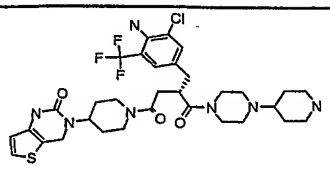
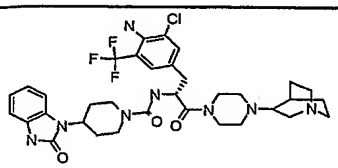
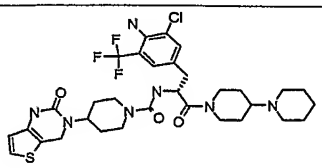
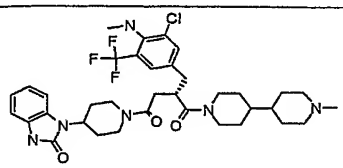
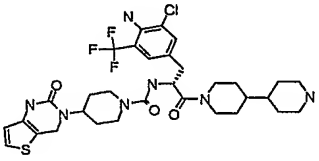
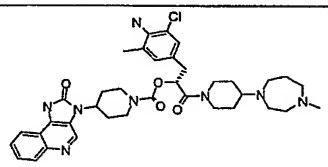
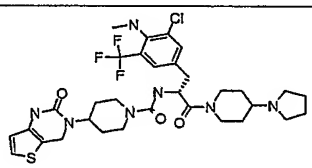
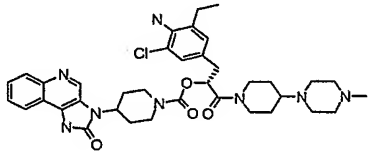
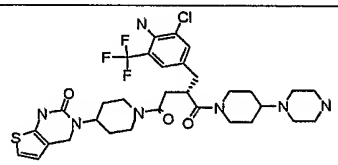
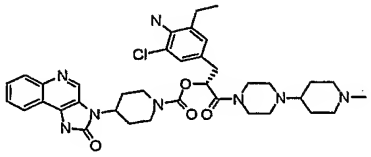
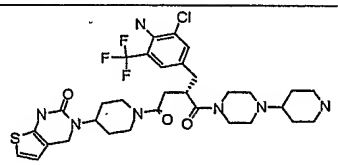
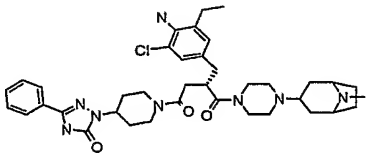
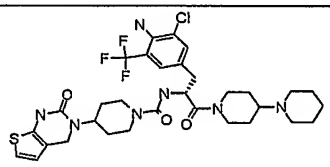
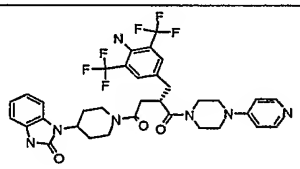
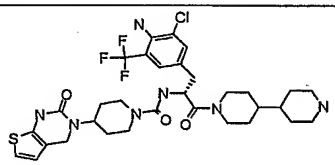
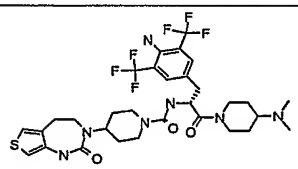
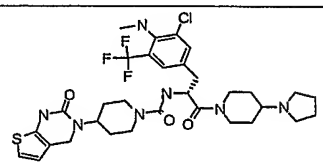
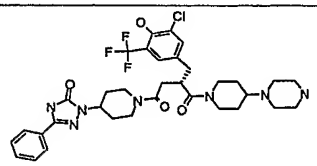
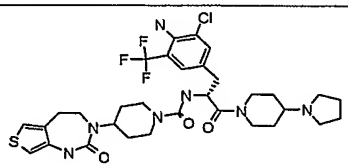
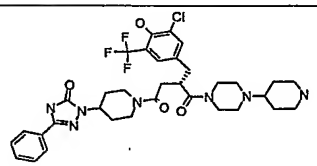
961		1111	
962		1112	
963		1113	
964		1114	
965		1115	
966		1116	
967		1117	
968		1118	
969		1119	
970		1120	

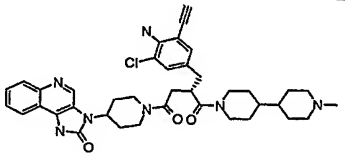
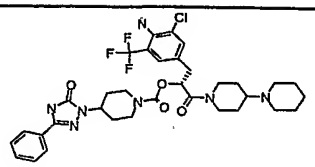
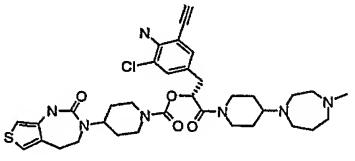
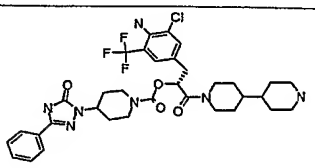
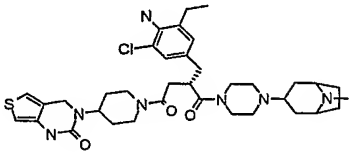
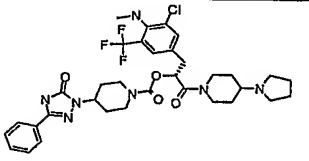
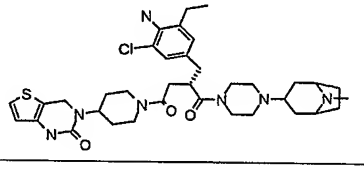
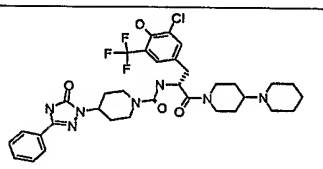
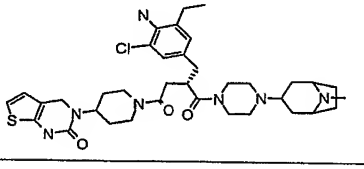
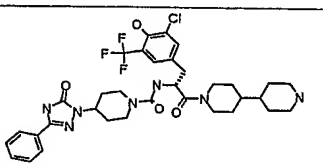
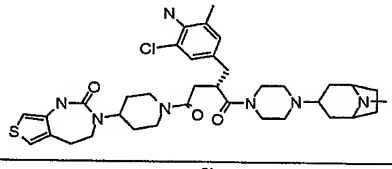
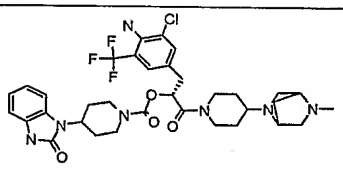
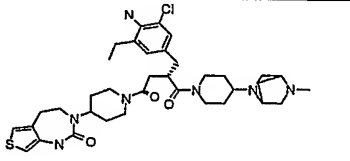
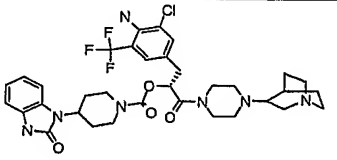
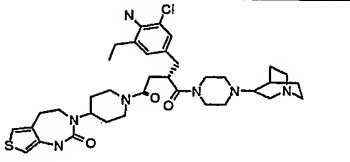
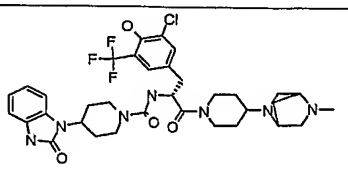
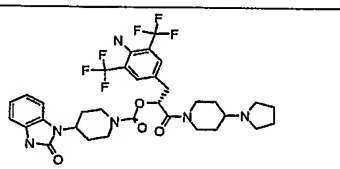
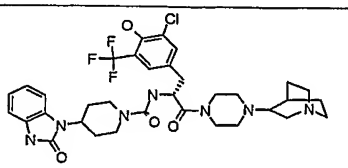
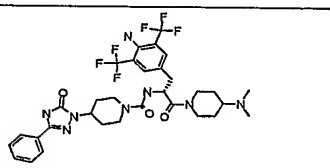
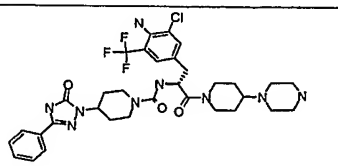
971		1121	
972		1122	
973		1123	
974		1124	
975		1125	
976		1126	
977		1127	
978		1128	
979		1129	
980		1130	

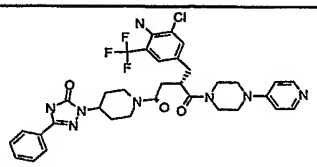
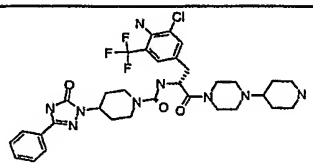
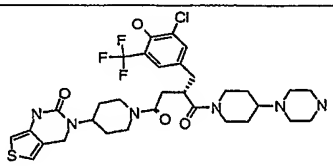
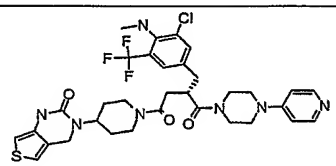
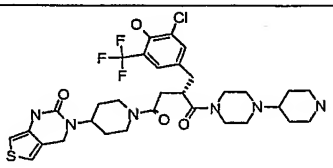
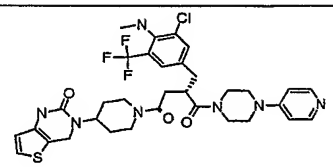
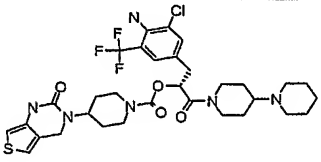
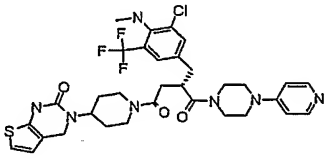
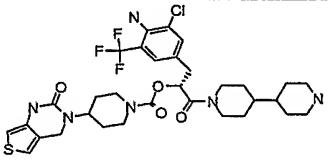
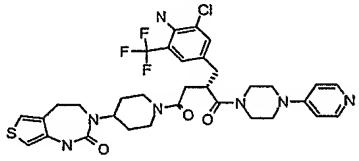
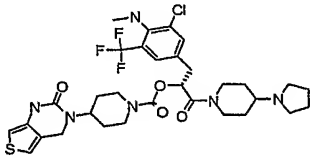
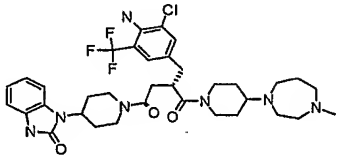
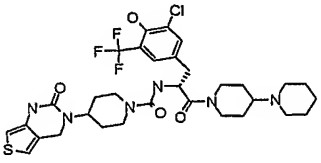
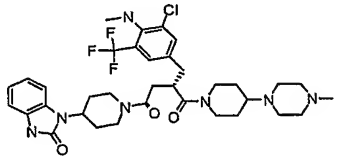
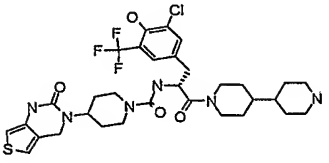
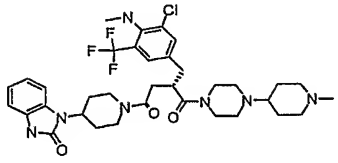
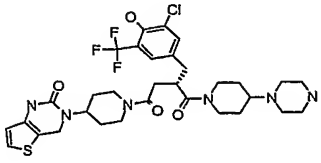
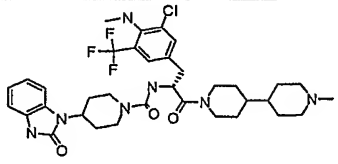
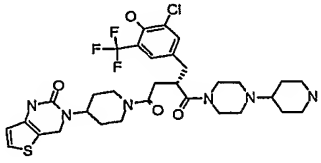
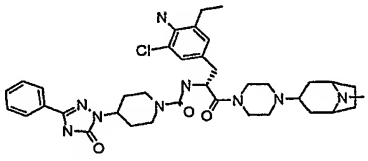
981		1131	
982		1132	
983		1133	
984		1134	
985		1135	
986		1136	
987		1137	
988		1138	
989		1139	
990		1140	

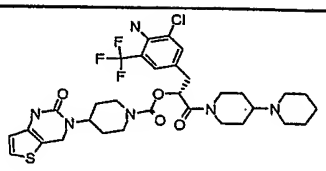
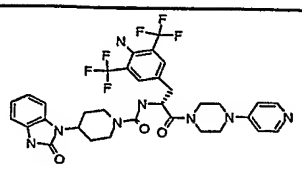
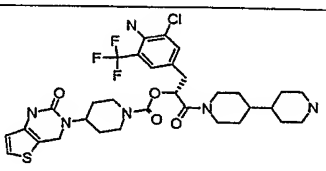
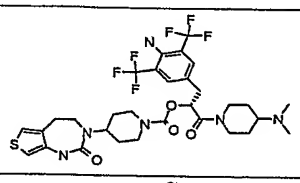
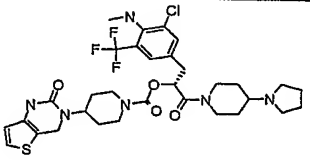
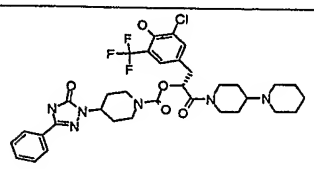
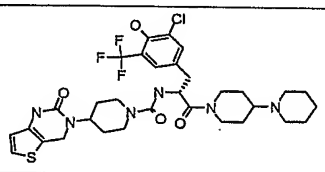
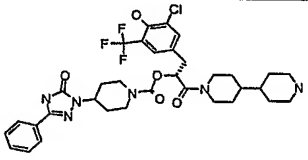
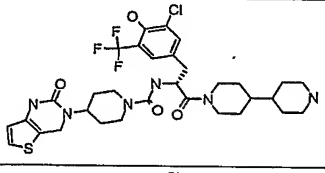
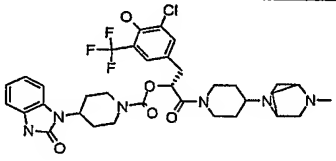
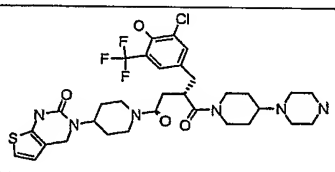
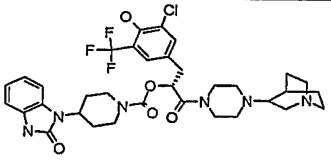
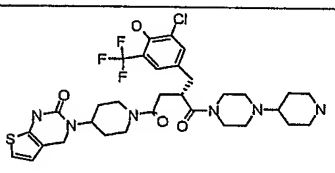
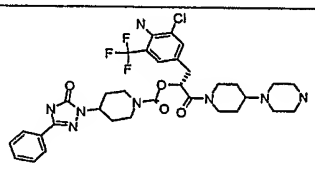
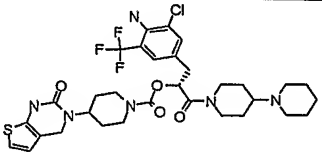
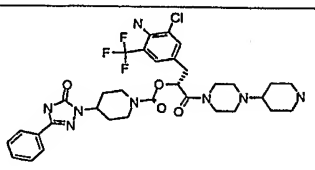
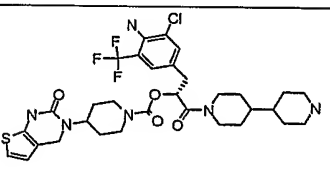
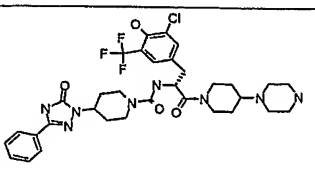
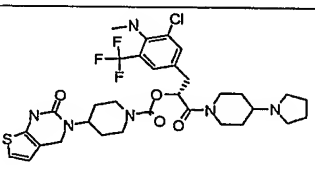
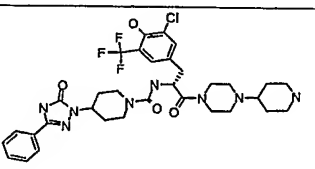
991		1141	
992		1142	
993		1143	
994		1144	
995		1145	
996		1146	
997		1147	
998		1148	
999		1149	
1000		1150	

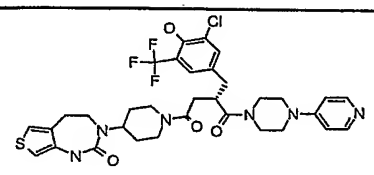
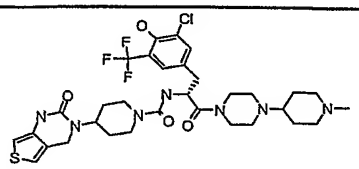
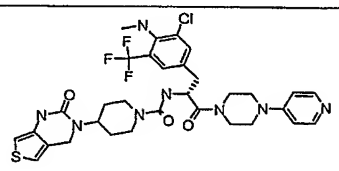
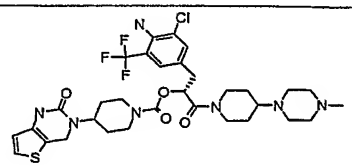
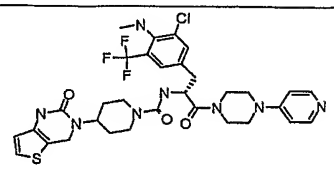
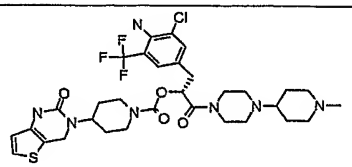
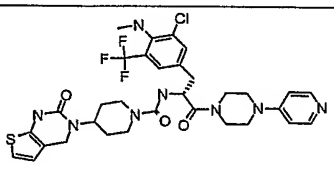
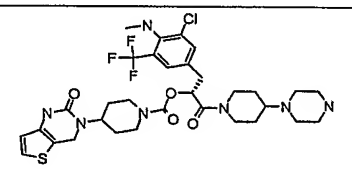
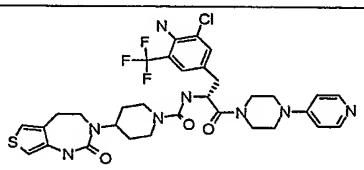
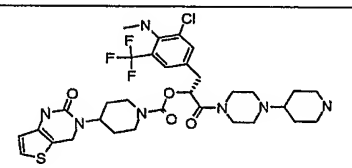
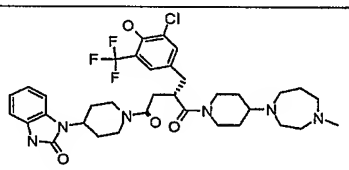
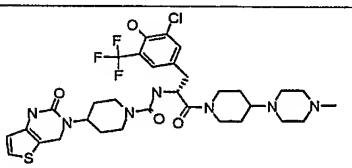
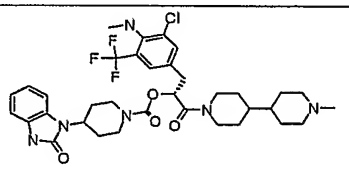
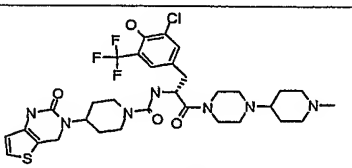
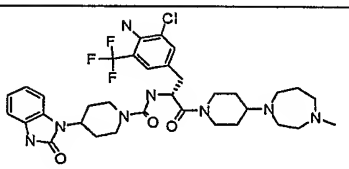
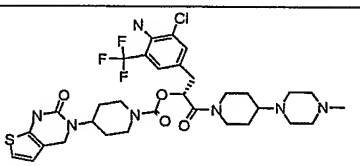
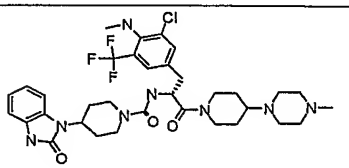
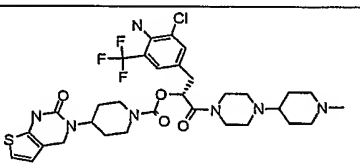
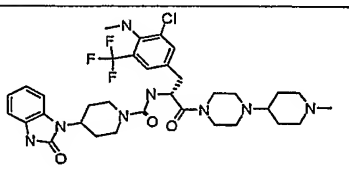
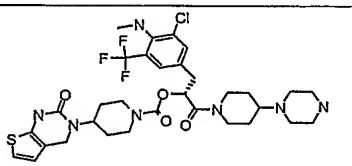
1001		1151	
1002		1152	
1003		1153	
1004		1154	
1005		1155	
1006		1156	
1007		1157	
1008		1158	
1009		1159	
1010		1160	

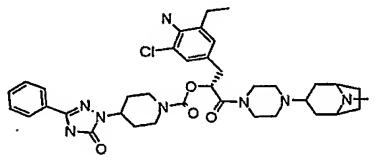
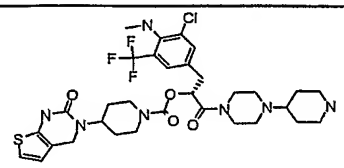
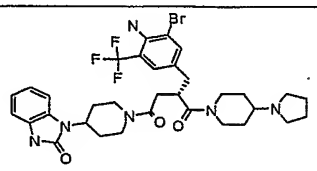
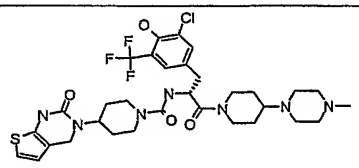
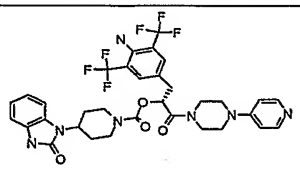
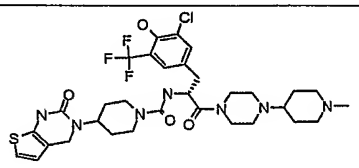
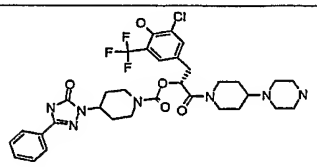
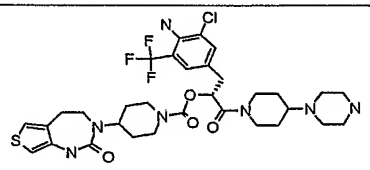
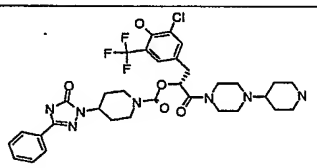
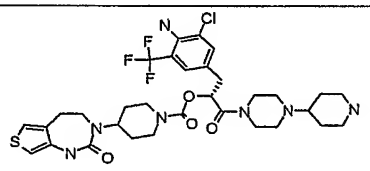
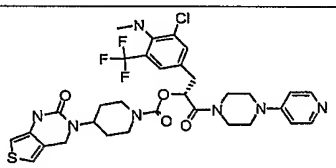
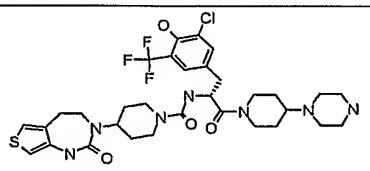
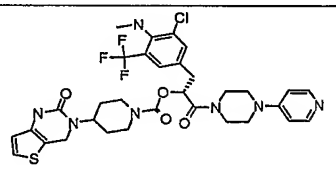
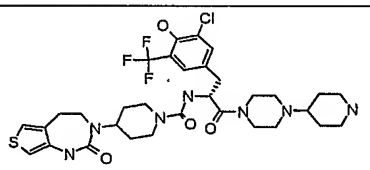
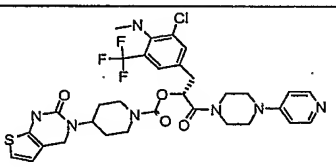
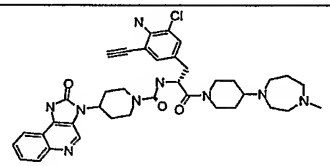
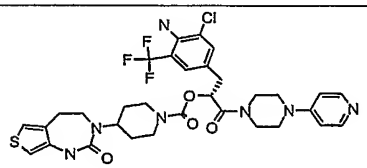
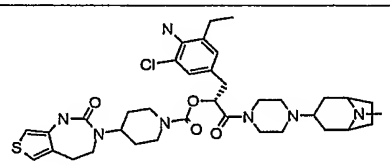
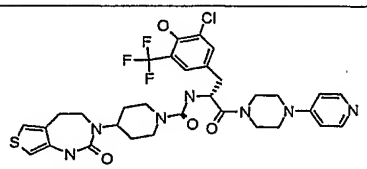
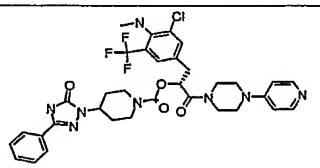
1011		1161	
1012		1162	
1013		1163	
1014		1164	
1015		1165	
1016		1166	
1017		1167	
1018		1168	
1019		1169	
1020		1170	

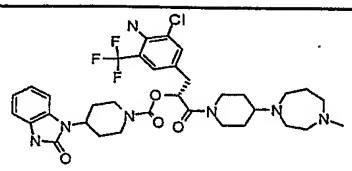
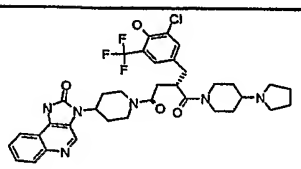
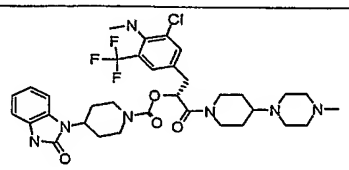
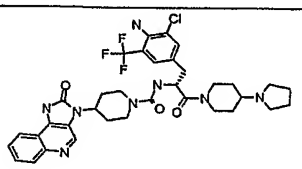
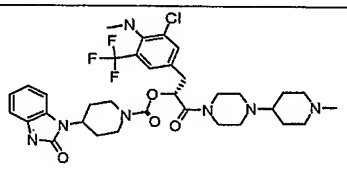
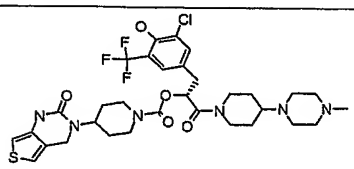
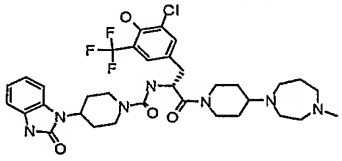
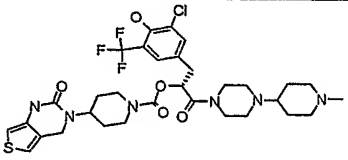
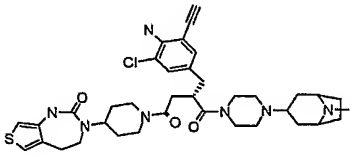
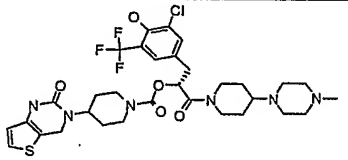
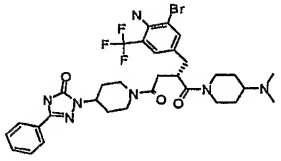
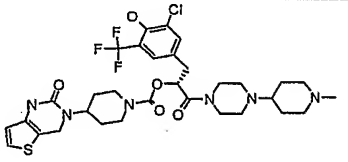
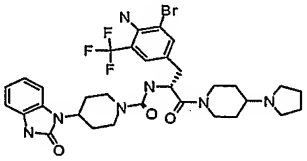
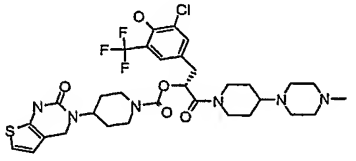
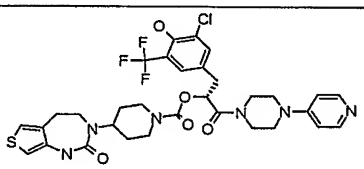
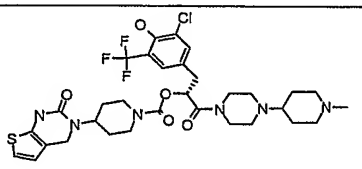
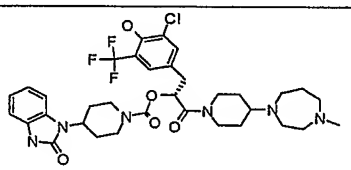
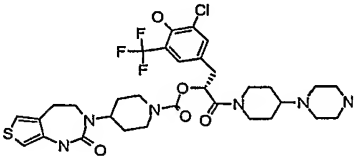
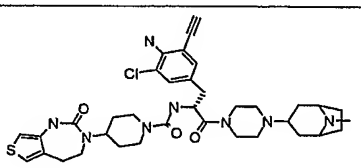
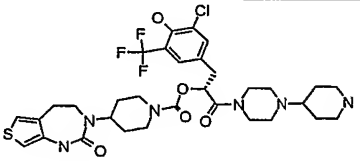
1021		1171	
1022		1172	
1023		1173	
1024		1174	
1025		1175	
1026		1176	
1027		1177	
1028		1178	
1029		1179	
1030		1180	

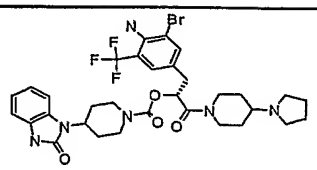
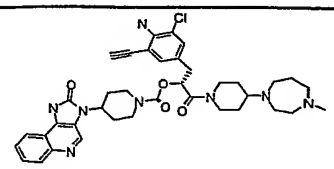
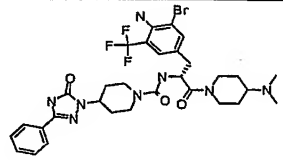
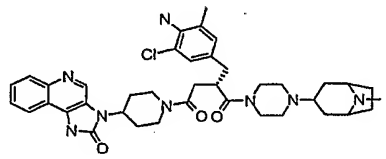
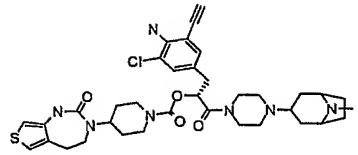
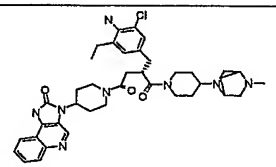
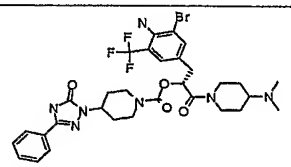
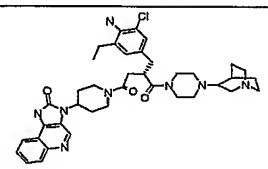
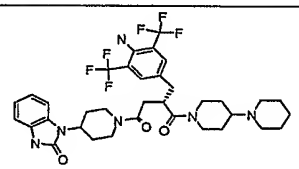
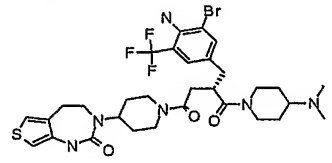
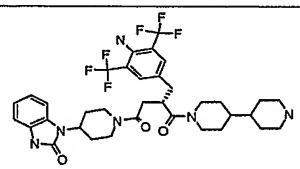
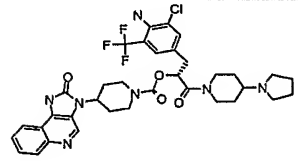
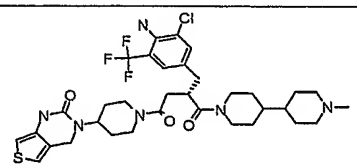
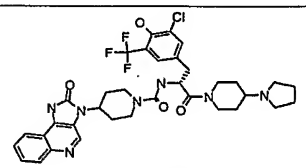
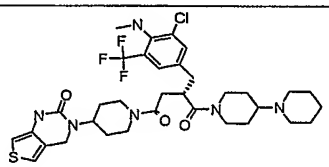
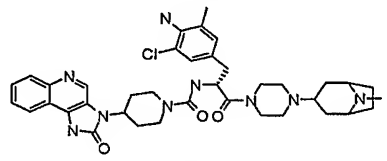
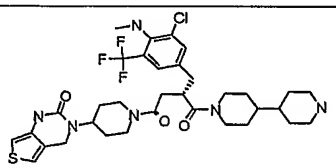
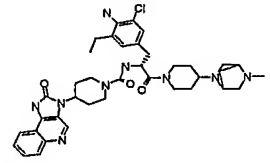
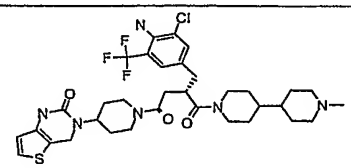
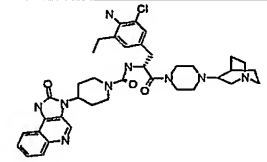
1031		1181	
1032		1182	
1033		1183	
1034		1184	
1035		1185	
1036		1186	
1037		1187	
1038		1188	
1039		1189	
1040		1190	

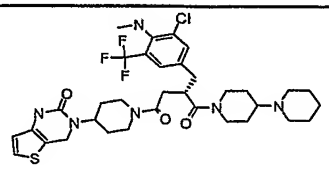
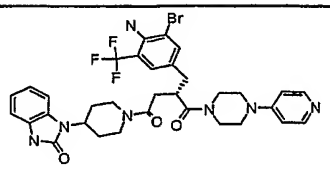
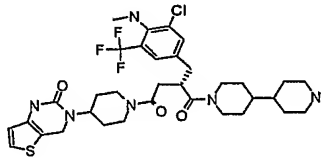
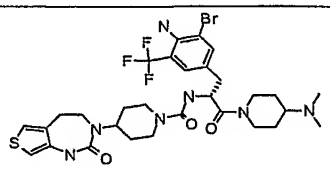
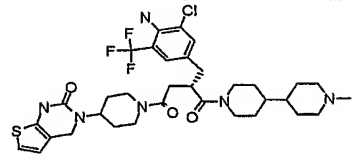
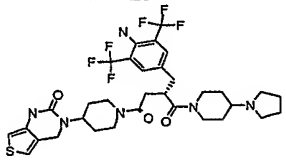
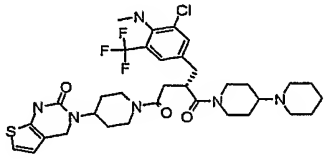
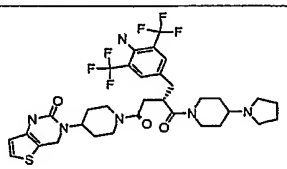
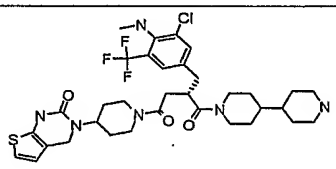
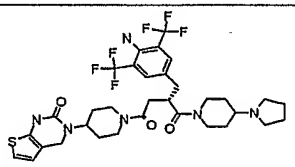
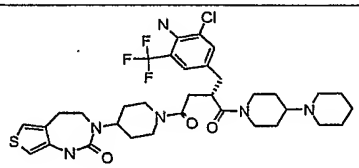
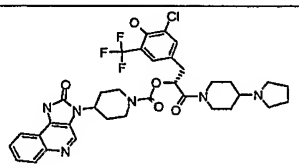
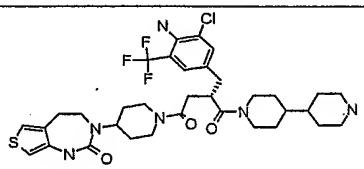
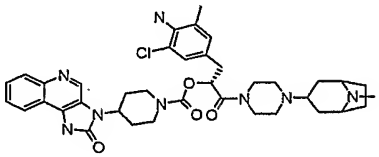
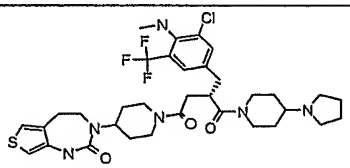
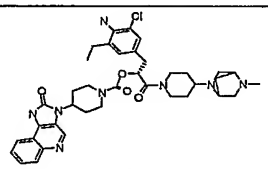
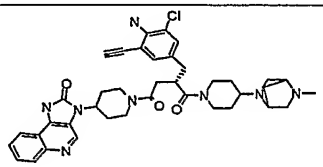
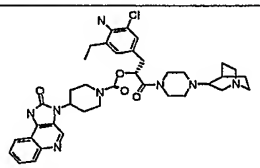
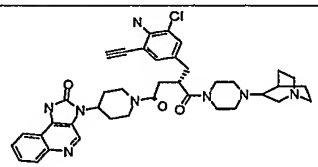
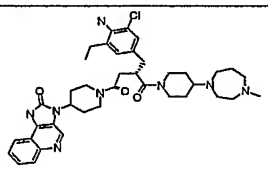
1041		1191	
1042		1192	
1043		1193	
1044		1194	
1045		1195	
1046		1196	
1047		1197	
1048		1198	
1049		1199	
1050		1200	

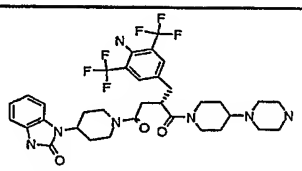
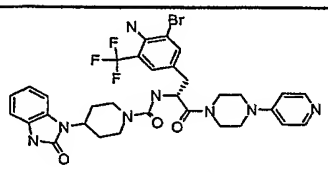
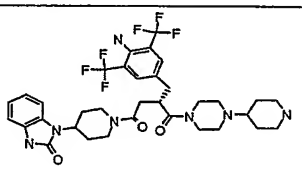
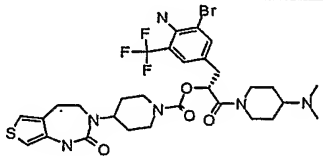
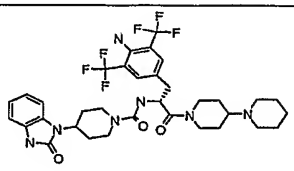
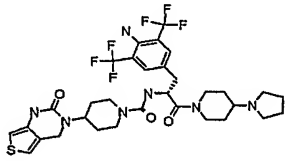
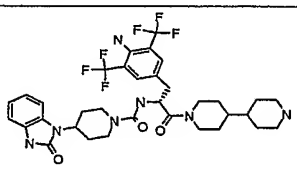
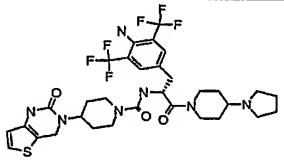
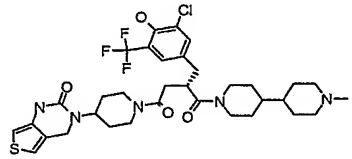
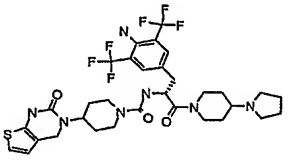
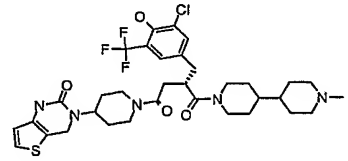
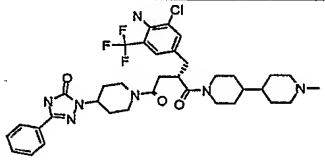
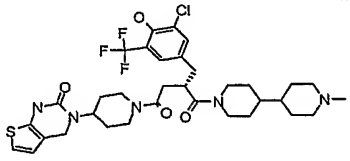
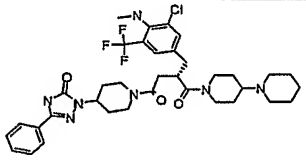
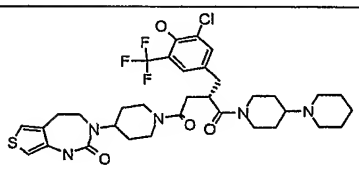
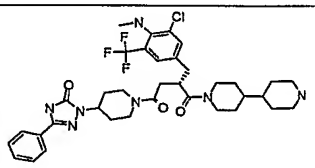
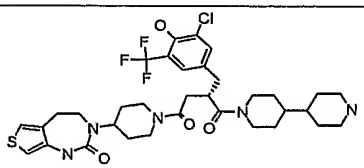
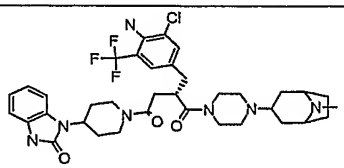
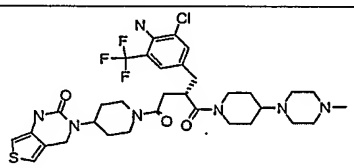
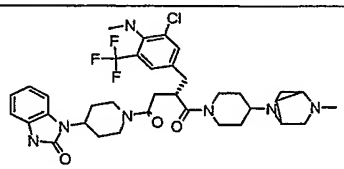
1201		1351	
1202		1352	
1203		1353	
1204		1354	
1205		1355	
1206		1356	
1207		1357	
1208		1358	
1209		1359	
1210		1360	

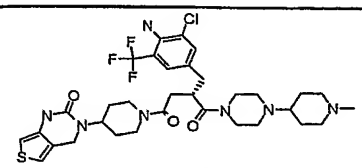
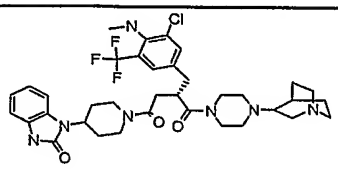
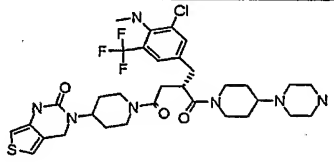
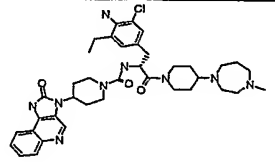
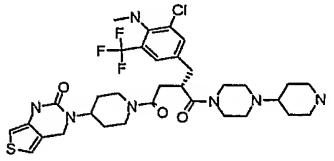
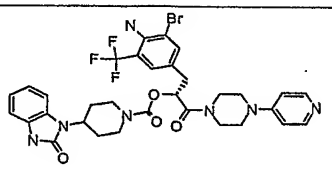
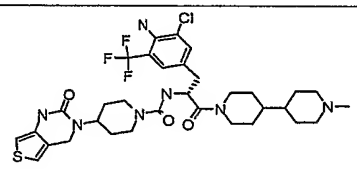
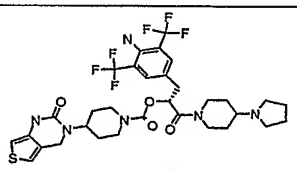
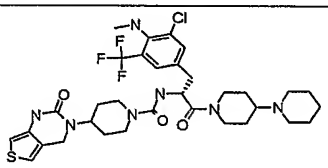
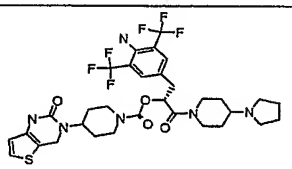
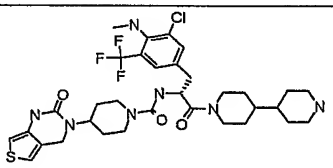
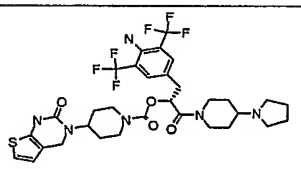
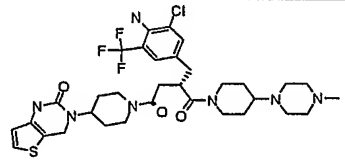
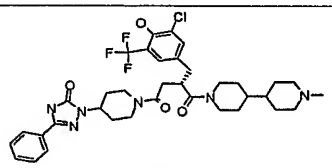
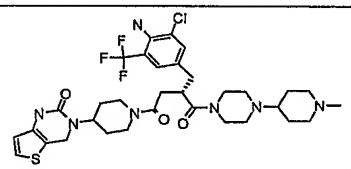
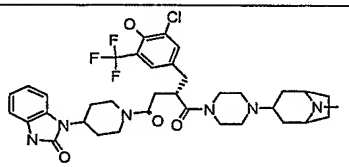
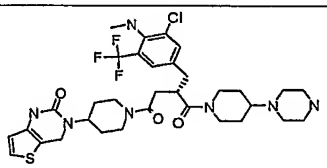
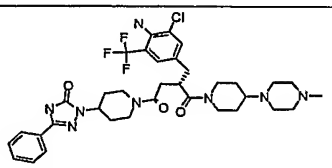
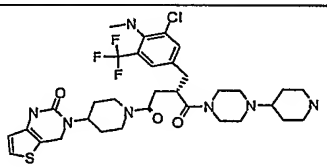
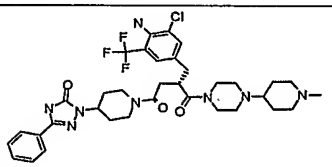
1211		1361	
1212		1362	
1213		1363	
1214		1364	
1215		1365	
1216		1366	
1217		1367	
1218		1368	
1219		1369	
1220		1370	

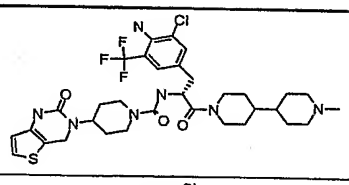
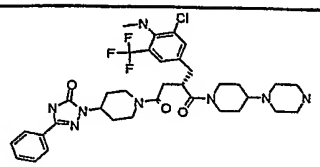
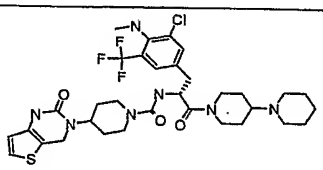
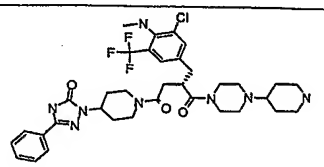
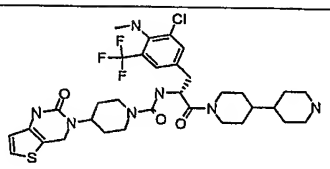
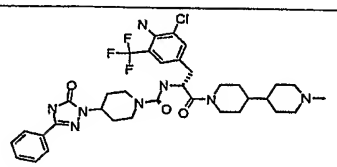
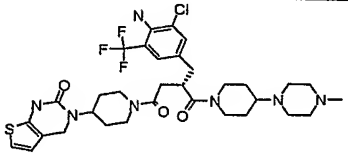
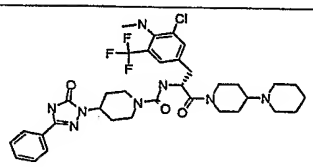
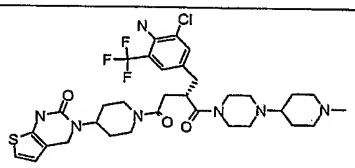
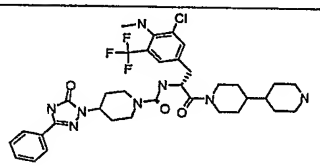
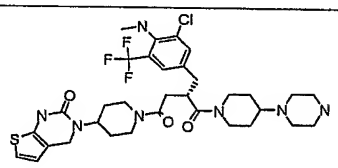
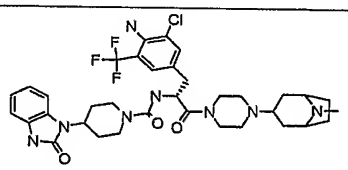
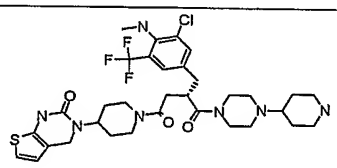
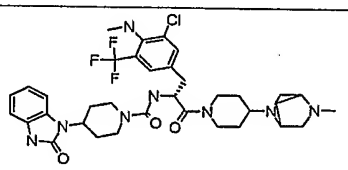
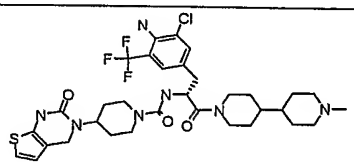
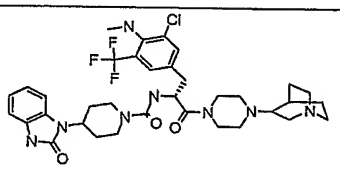
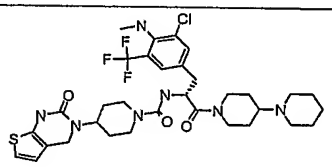
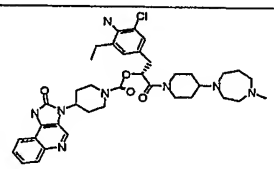
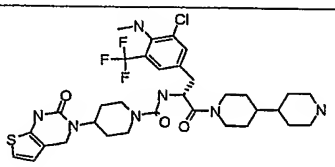
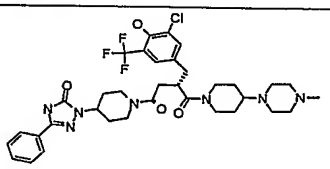
1221		1371	
1222		1372	
1223		1373	
1224		1374	
1225		1375	
1226		1376	
1227		1377	
1228		1378	
1229		1379	
1230		1380	

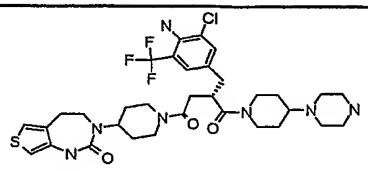
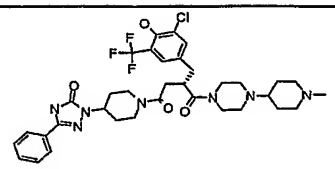
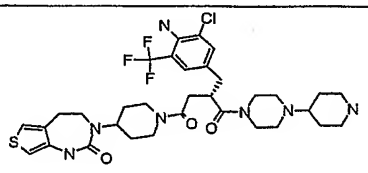
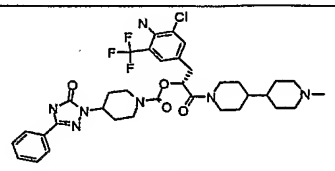
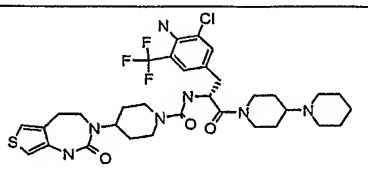
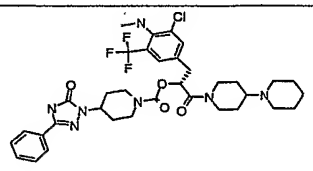
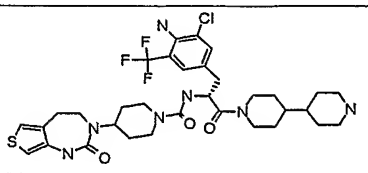
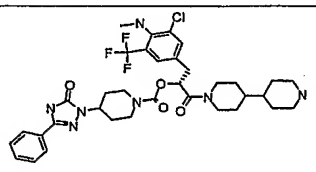
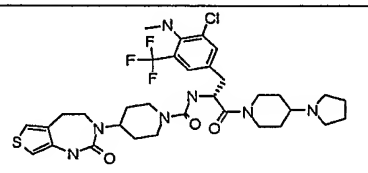
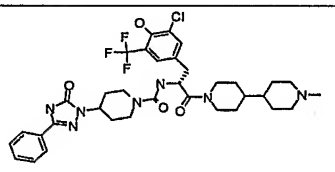
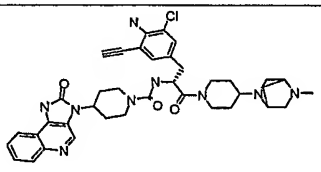
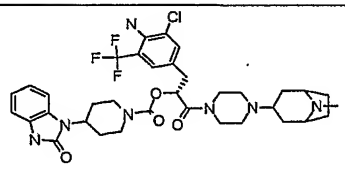
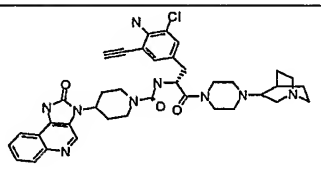
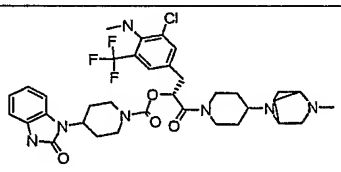
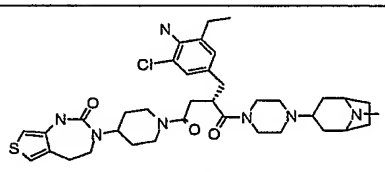
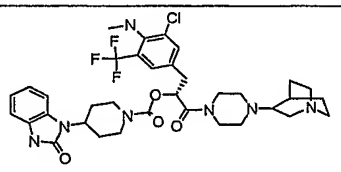
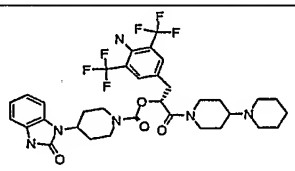
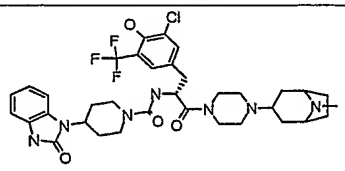
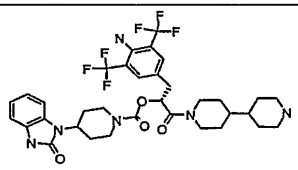
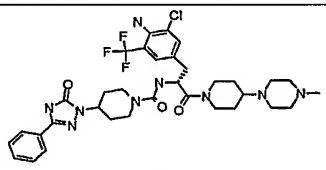
1231		1381	
1232		1382	
1233		1383	
1234		1384	
1235		1385	
1236		1386	
1237		1387	
1238		1388	
1239		1389	
1240		1390	

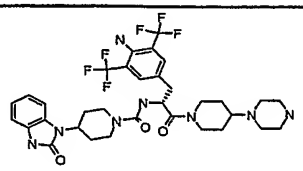
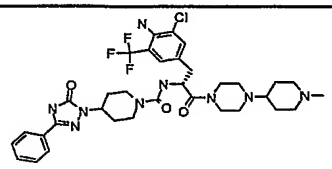
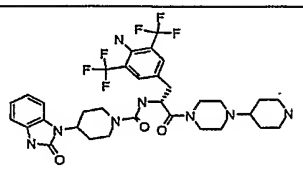
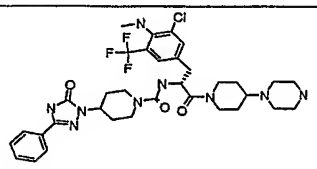
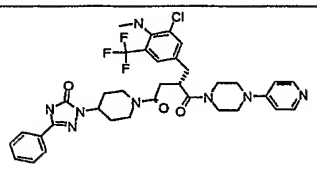
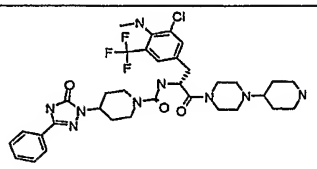
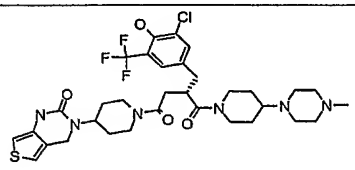
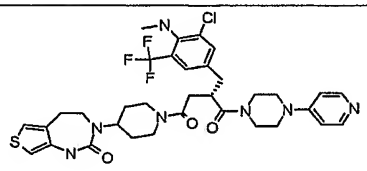
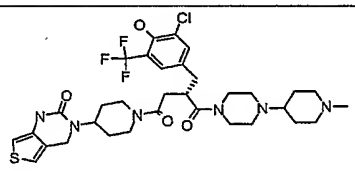
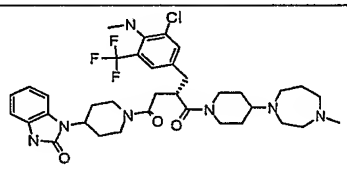
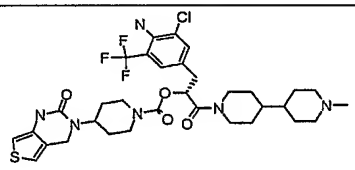
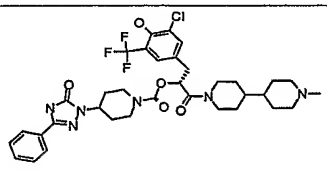
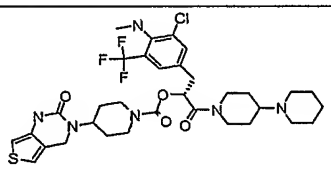
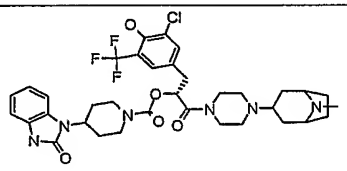
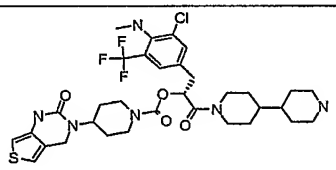
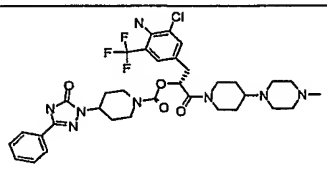
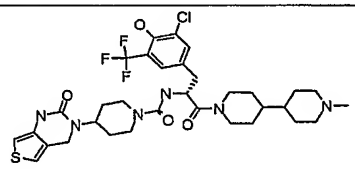
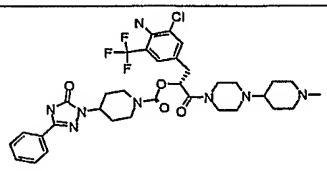
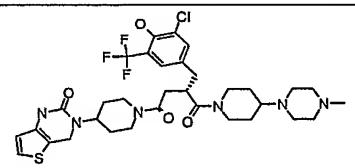
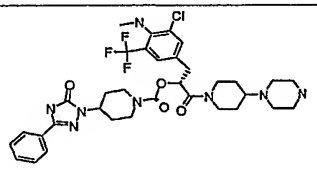
1241		1391	
1242		1392	
1243		1393	
1244		1394	
1245		1395	
1246		1396	
1247		1397	
1248		1398	
1249		1399	
1250		1400	

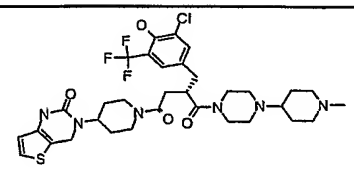
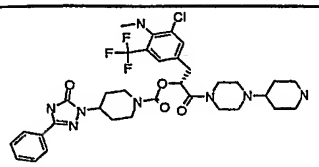
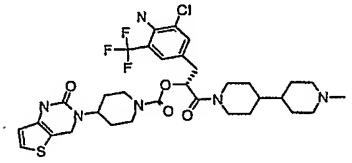
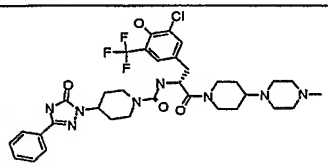
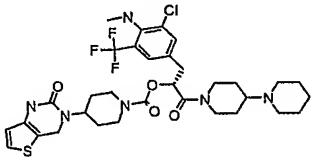
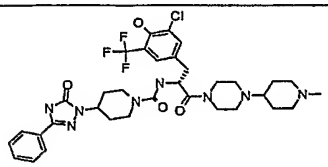
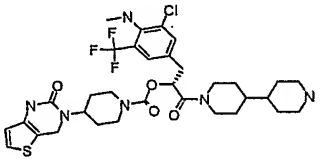
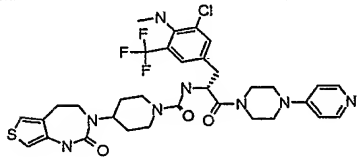
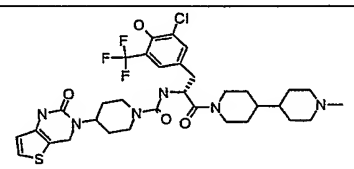
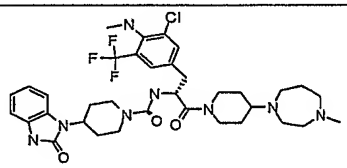
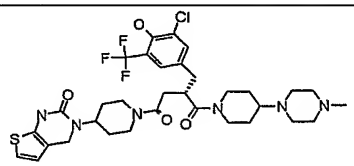
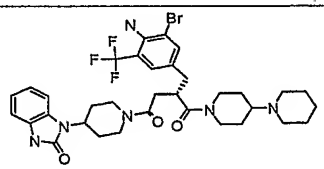
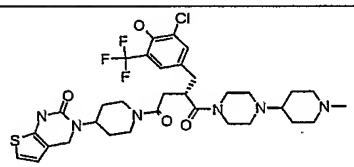
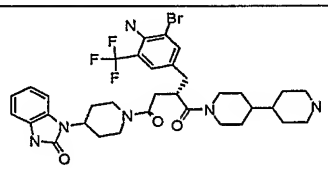
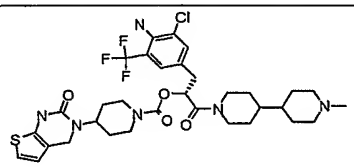
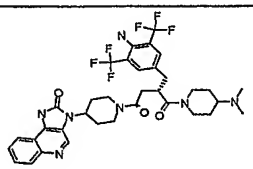
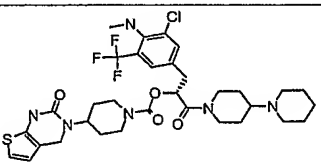
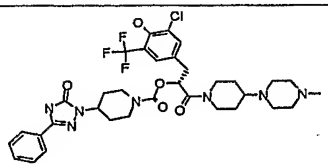
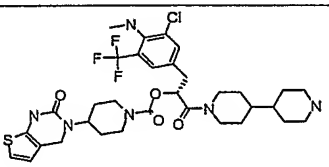
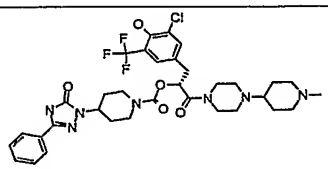
1251		1401	
1252		1402	
1253		1403	
1254		1404	
1255		1405	
1256		1406	
1257		1407	
1258		1408	
1259		1409	
1260		1410	

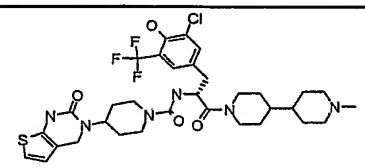
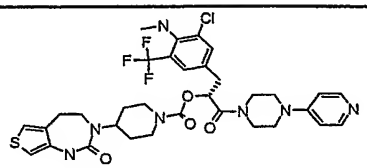
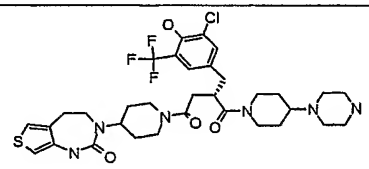
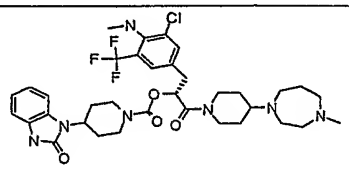
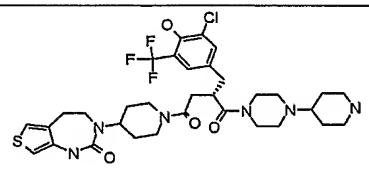
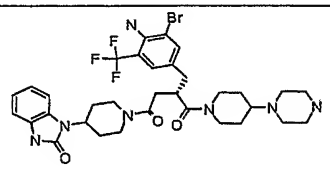
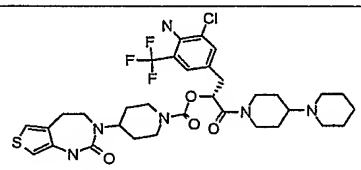
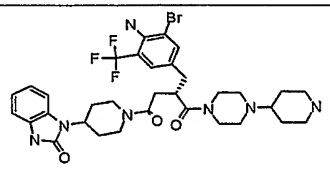
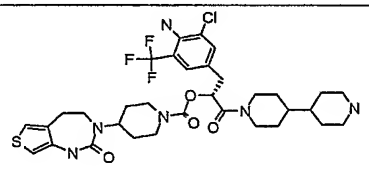
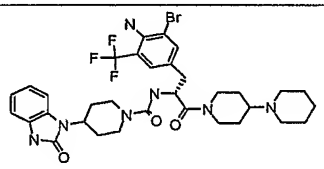
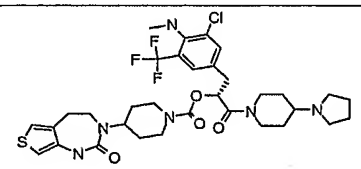
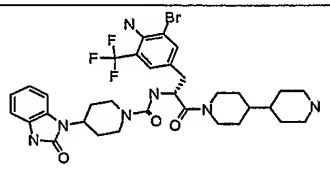
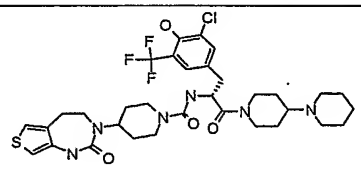
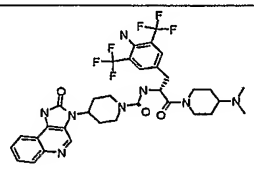
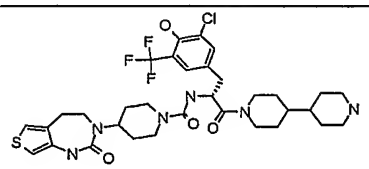
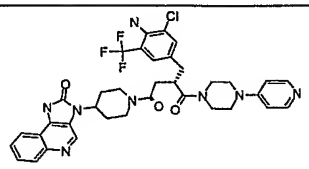
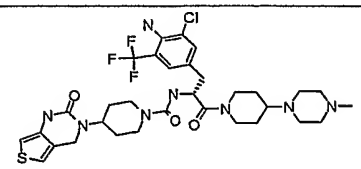
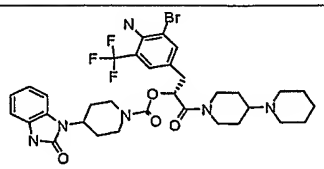
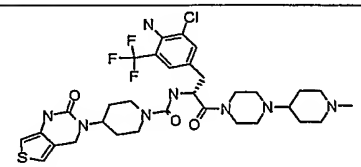
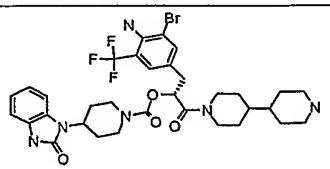
1261		1411	
1262		1412	
1263		1413	
1264		1414	
1265		1415	
1266		1416	
1267		1417	
1268		1418	
1269		1419	
1270		1420	

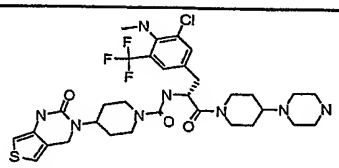
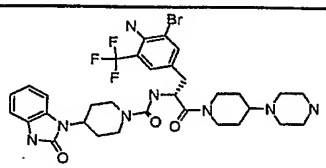
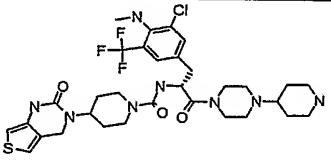
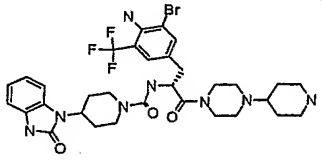
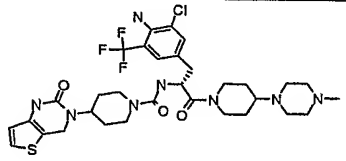
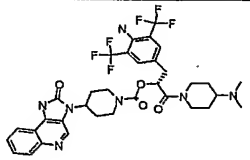
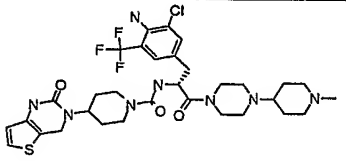
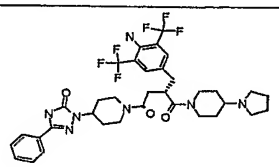
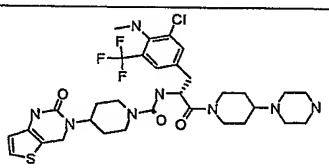
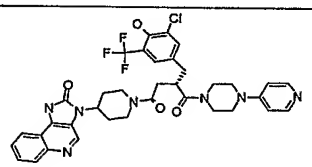
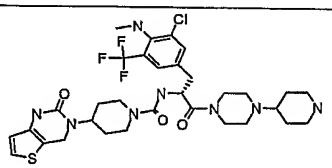
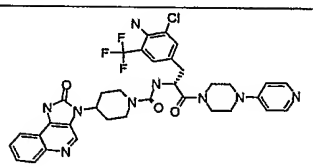
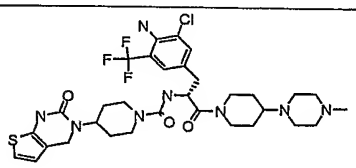
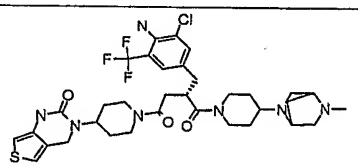
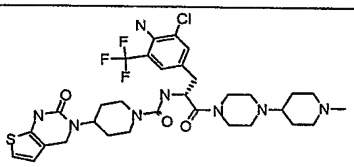
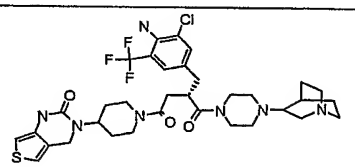
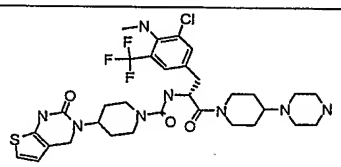
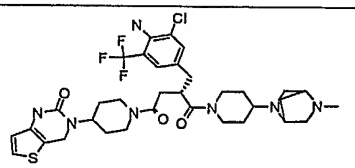
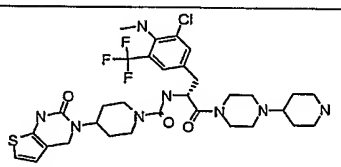
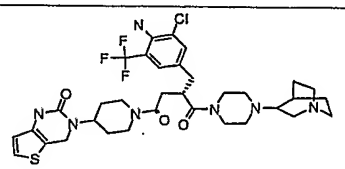
1271		1421	
1272		1422	
1273		1423	
1274		1424	
1275		1425	
1276		1426	
1277		1427	
1278		1428	
1279		1429	
1280		1430	

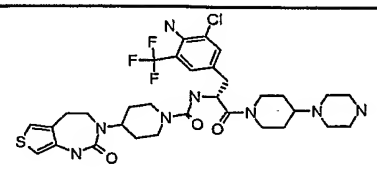
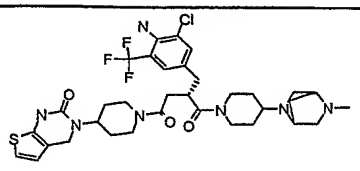
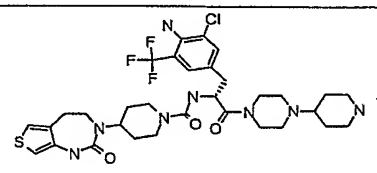
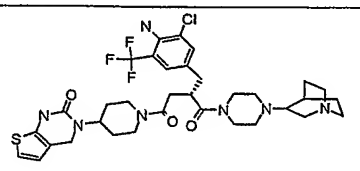
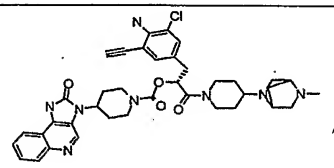
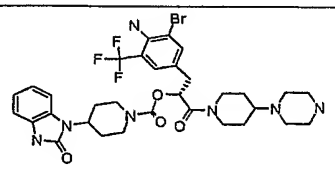
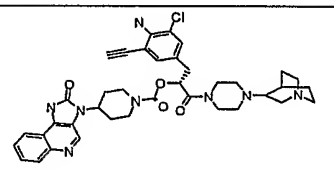
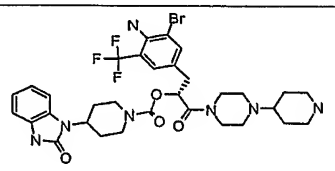
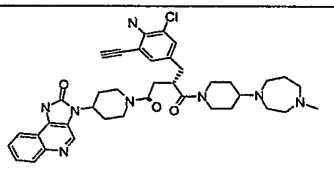
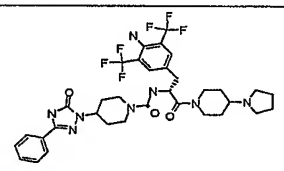
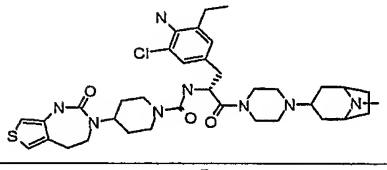
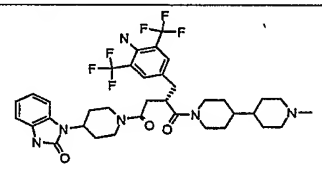
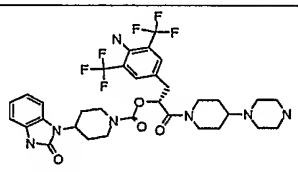
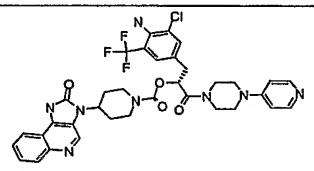
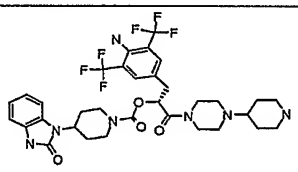
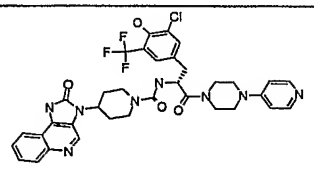
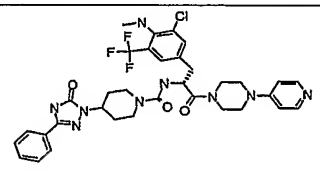
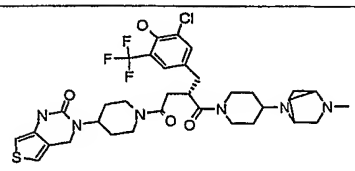
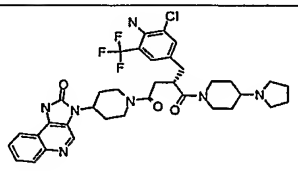
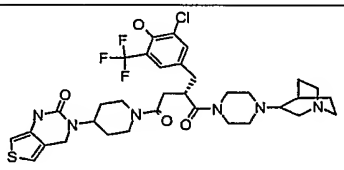
1281		1431	
1282		1432	
1283		1433	
1284		1434	
1285		1435	
1286		1436	
1287		1437	
1288		1438	
1289		1439	
1290		1440	

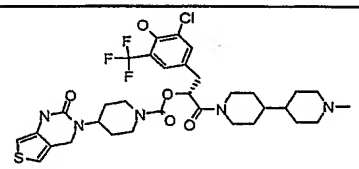
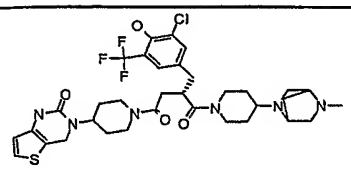
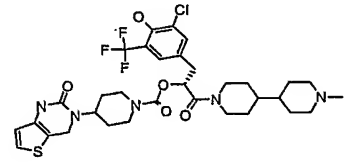
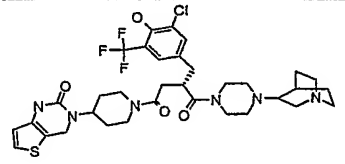
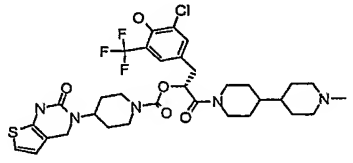
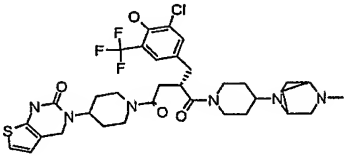
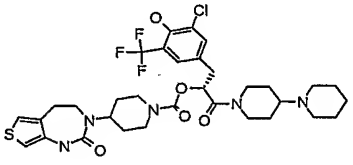
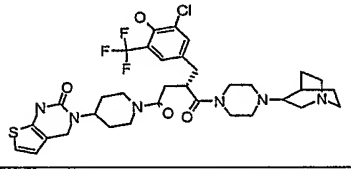
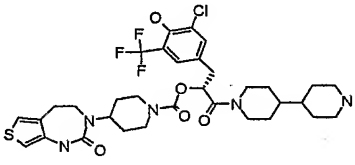
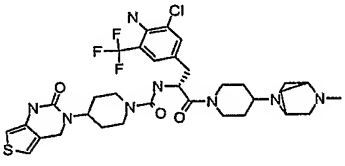
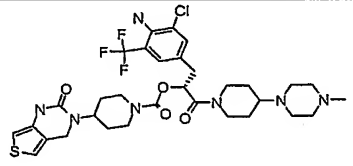
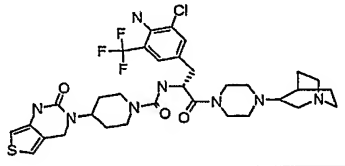
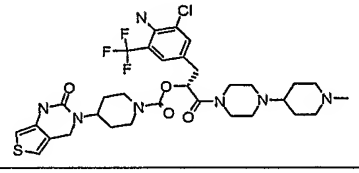
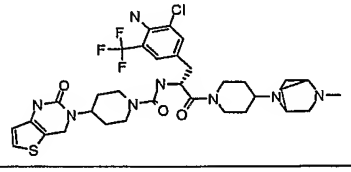
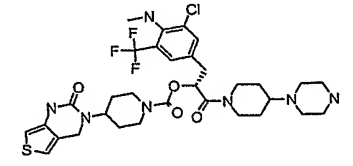
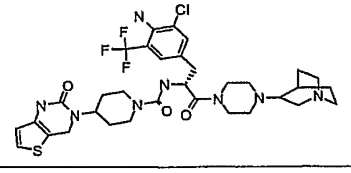
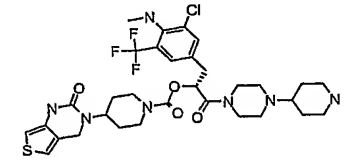
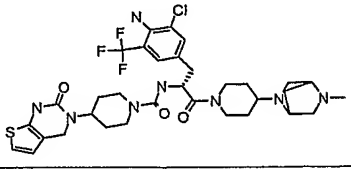
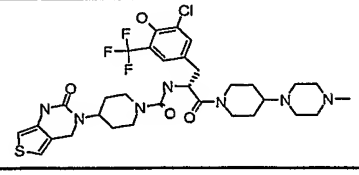
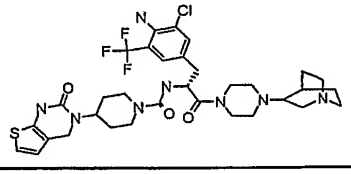
1291		1441	
1292		1442	
1293		1443	
1294		1444	
1295		1445	
1296		1446	
1297		1447	
1298		1448	
1299		1449	
1300		1450	

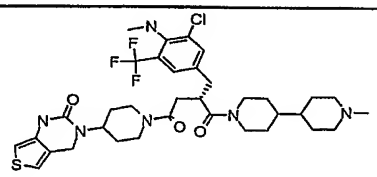
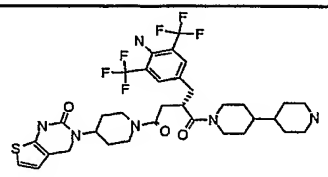
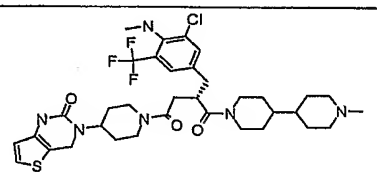
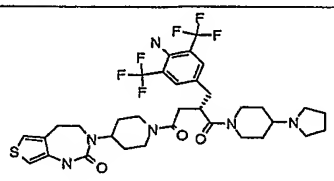
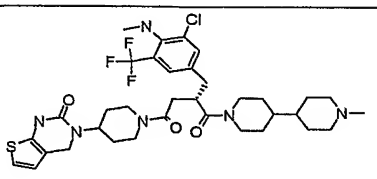
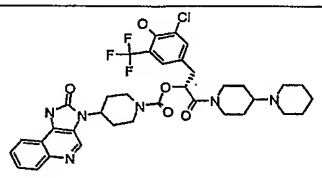
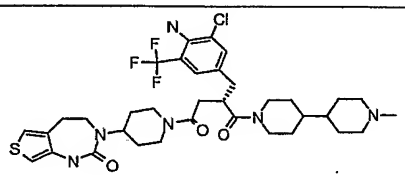
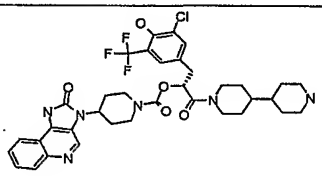
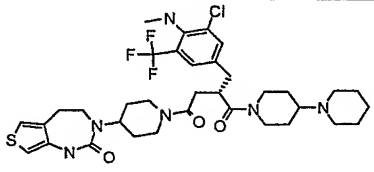
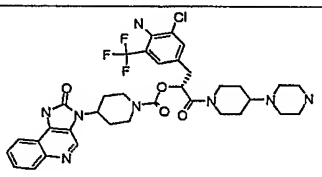
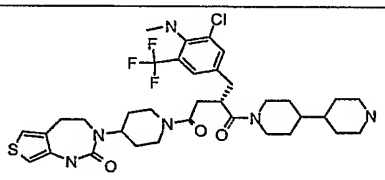
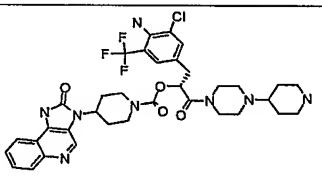
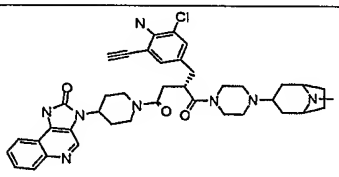
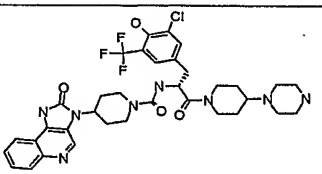
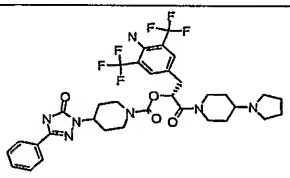
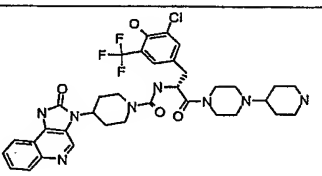
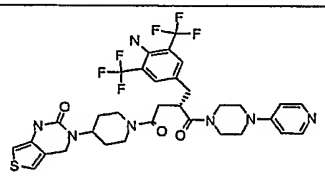
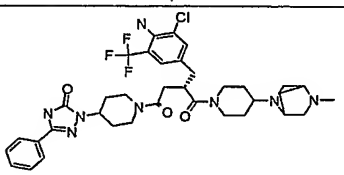
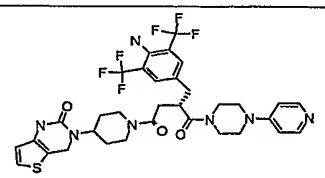
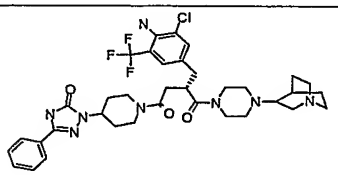
1301		1451	
1302		1452	
1303		1453	
1304		1454	
1305		1455	
1306		1456	
1307		1457	
1308		1458	
1309		1459	
1310		1460	

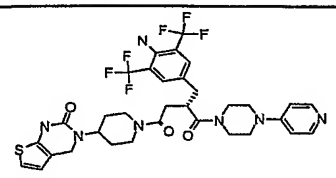
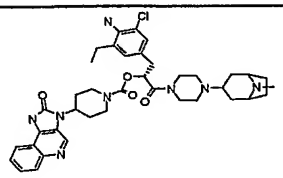
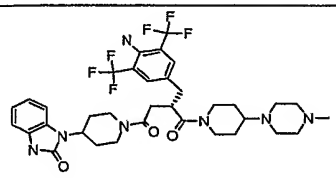
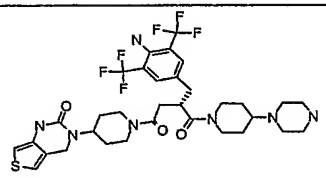
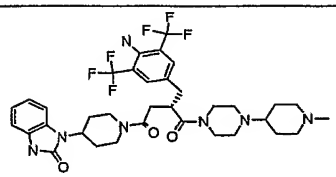
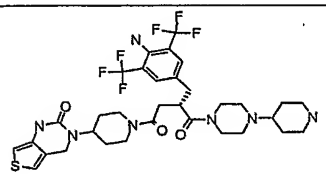
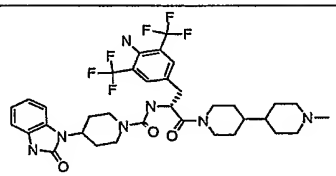
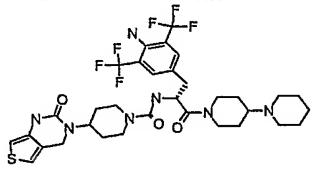
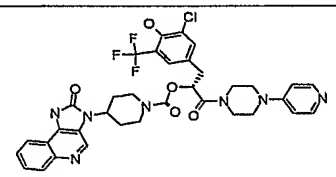
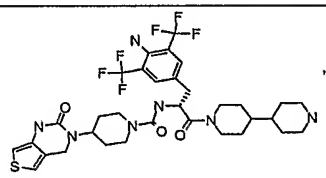
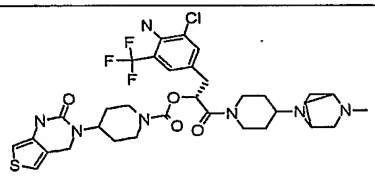
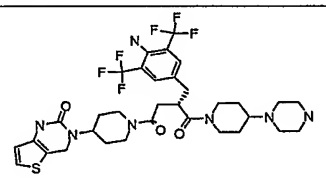
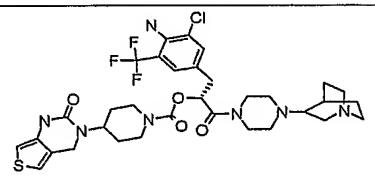
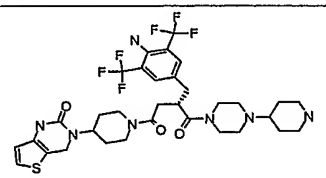
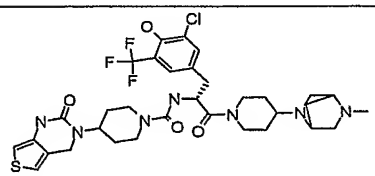
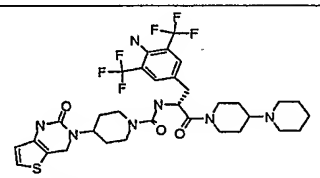
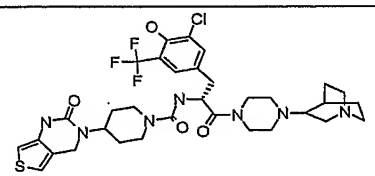
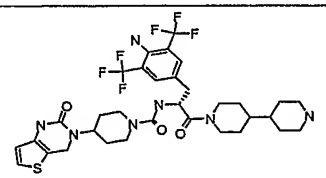
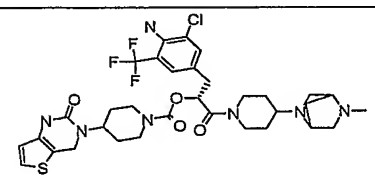
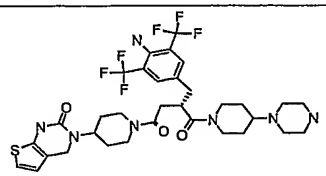
1311		1461	
1312		1462	
1313		1463	
1314		1464	
1315		1465	
1316		1466	
1317		1467	
1318		1468	
1319		1469	
1320		1470	

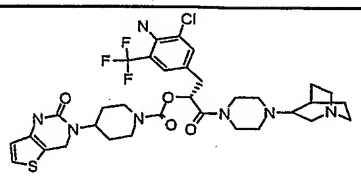
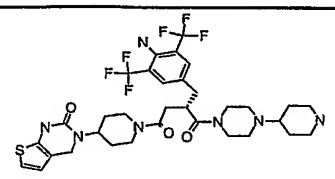
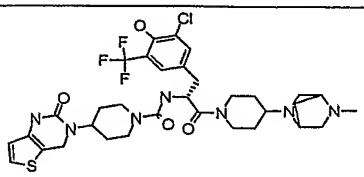
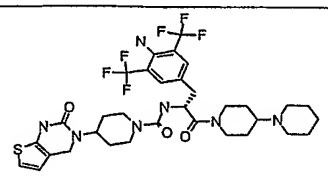
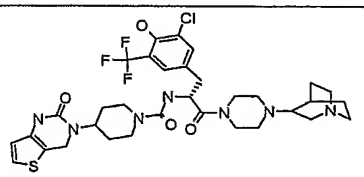
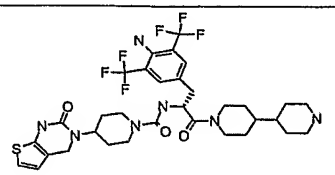
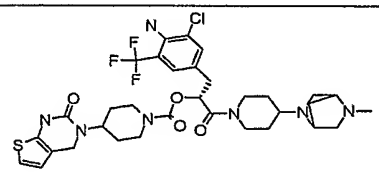
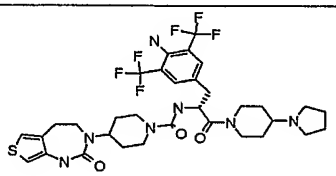
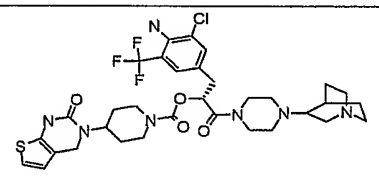
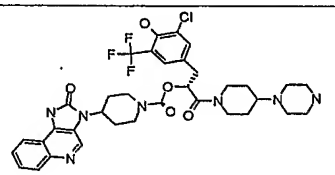
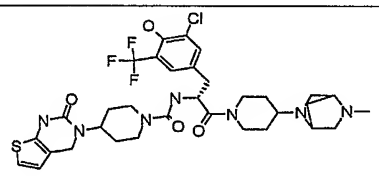
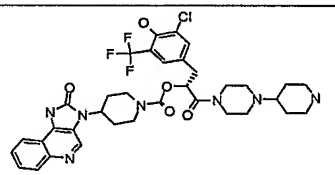
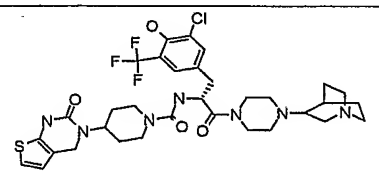
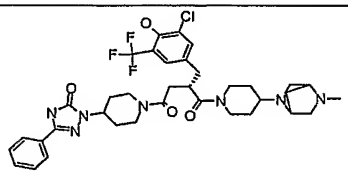
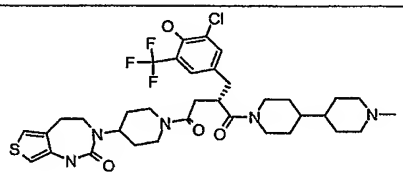
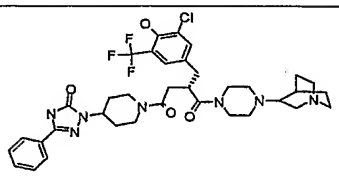
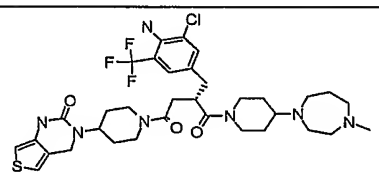
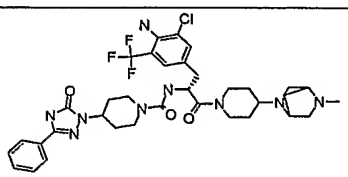
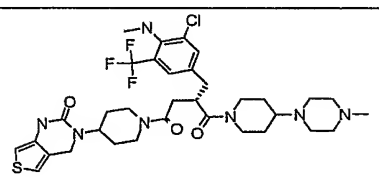
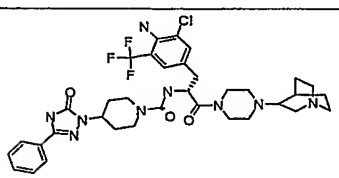
1321		1471	
1322		1472	
1323		1473	
1324		1474	
1325		1475	
1326		1476	
1327		1477	
1328		1478	
1329		1479	
1330		1480	

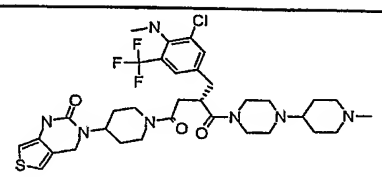
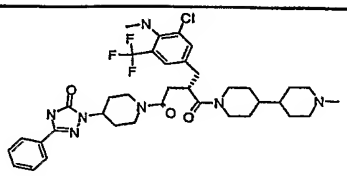
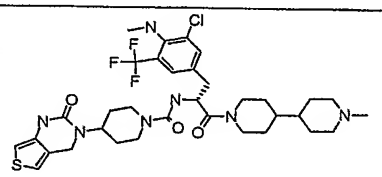
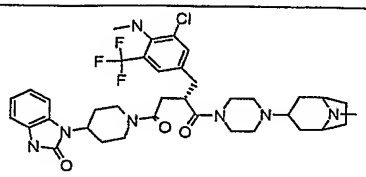
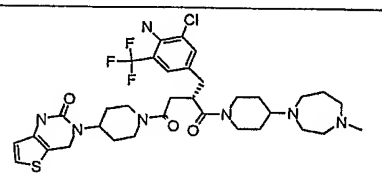
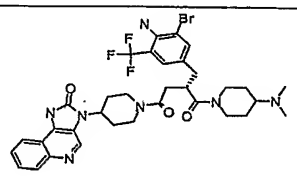
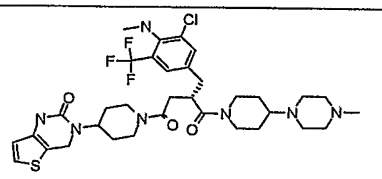
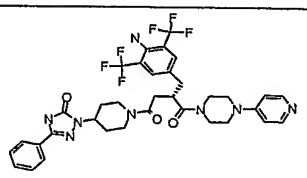
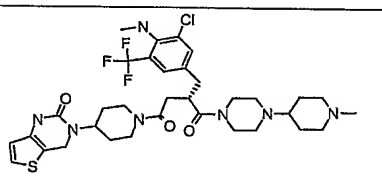
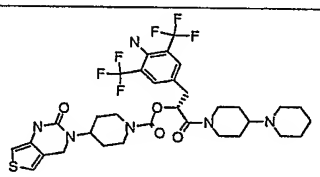
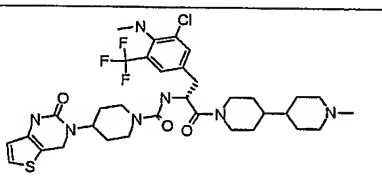
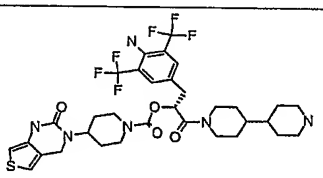
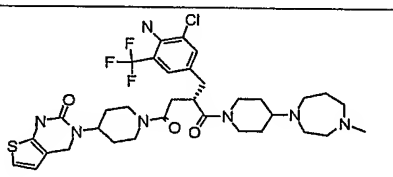
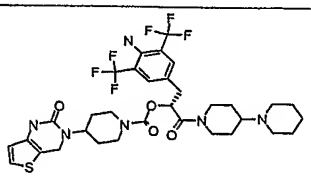
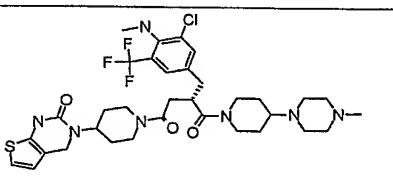
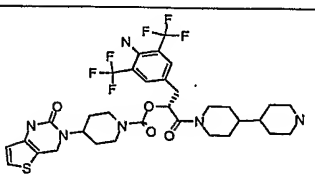
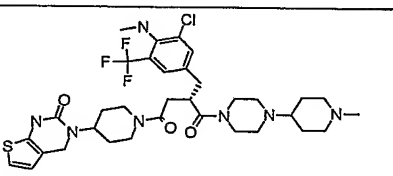
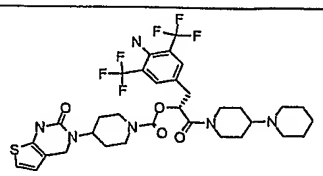
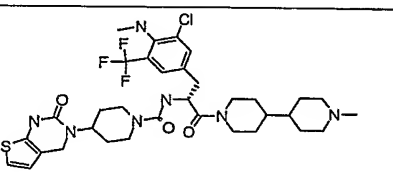
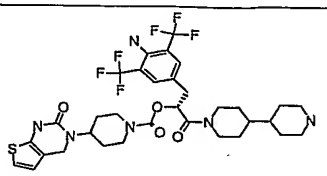
1331		1481	
1332		1482	
1333		1483	
1334		1484	
1335		1485	
1336		1486	
1337		1487	
1338		1488	
1339		1489	
1340		1490	

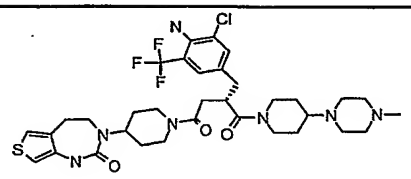
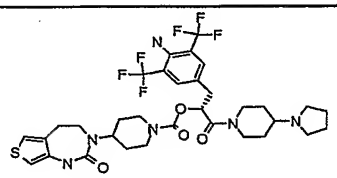
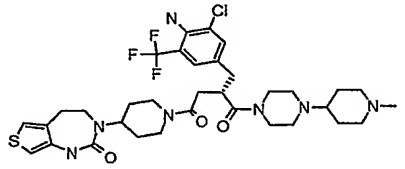
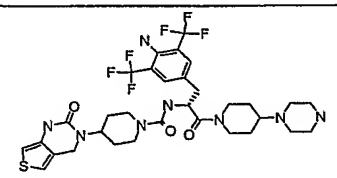
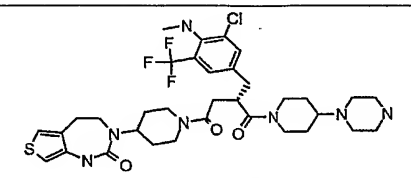
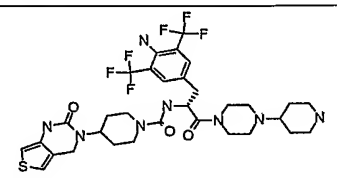
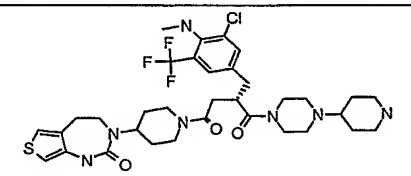
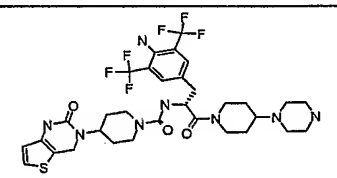
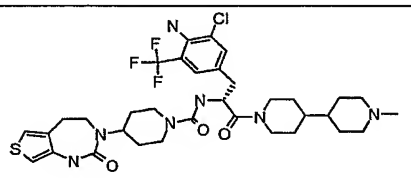
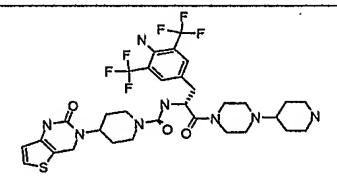
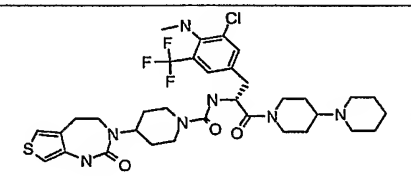
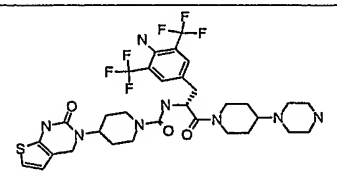
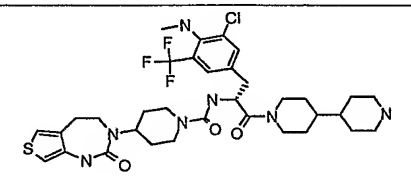
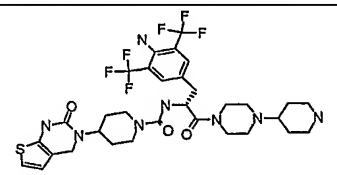
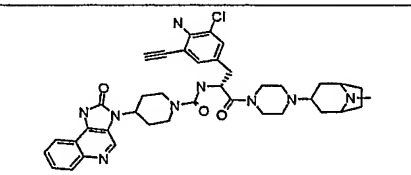
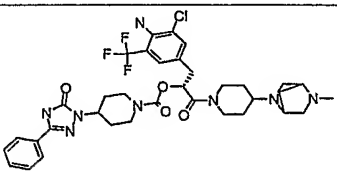
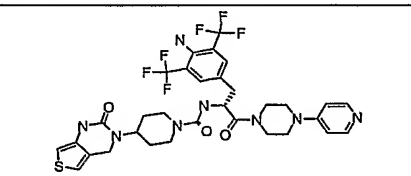
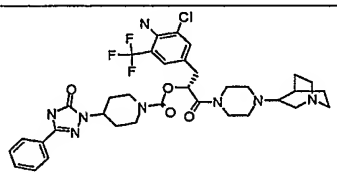
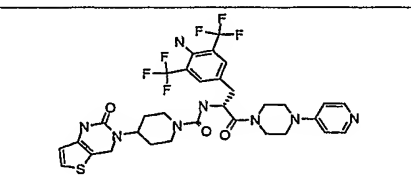
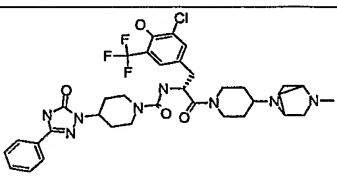
1341		1491	
1342		1492	
1343		1493	
1344		1494	
1345		1495	
1346		1496	
1347		1497	
1348		1498	
1349		1499	
1350		1500	

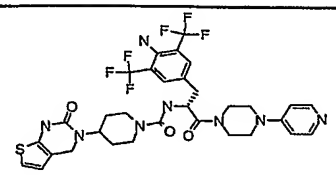
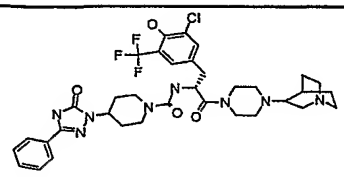
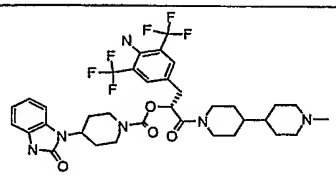
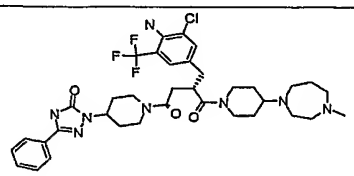
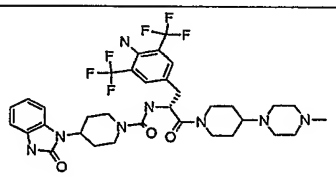
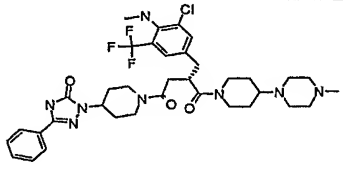
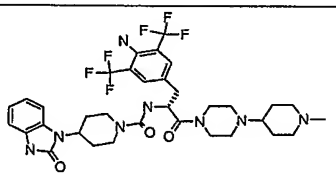
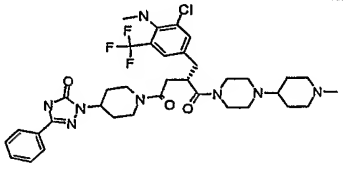
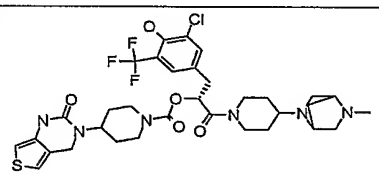
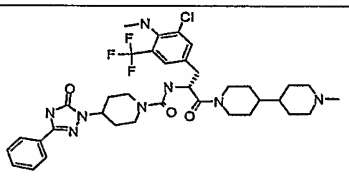
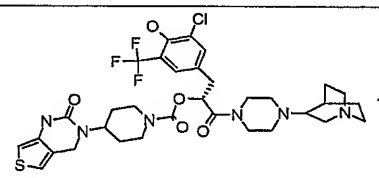
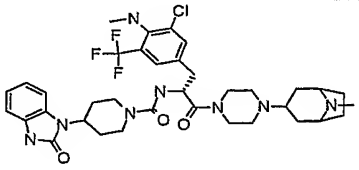
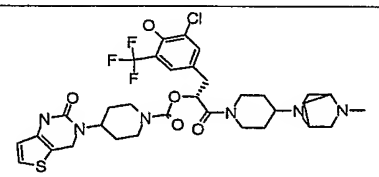
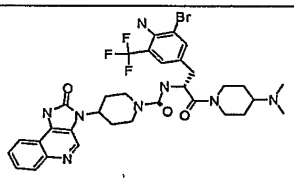
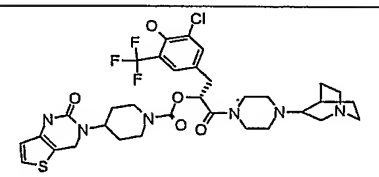
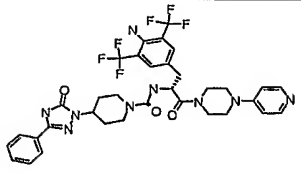
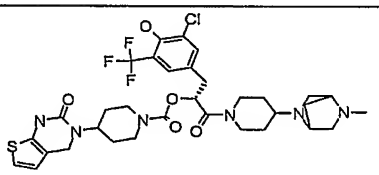
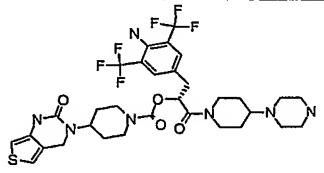
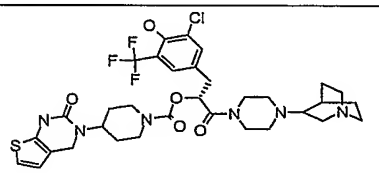
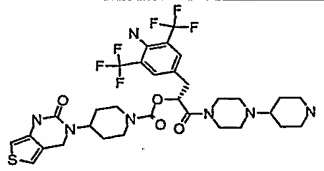
1501		1651	
1502		1652	
1503		1653	
1504		1654	
1505		1655	
1506		1656	
1507		1657	
1508		1658	
1509		1659	
1510		1660	

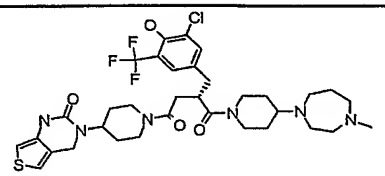
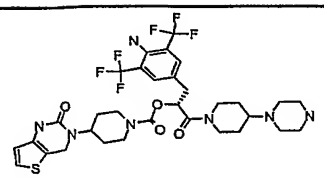
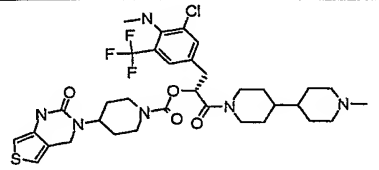
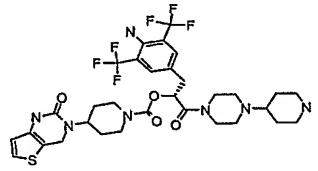
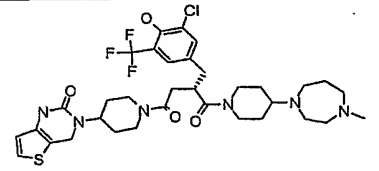
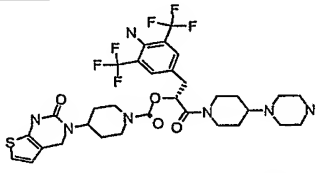
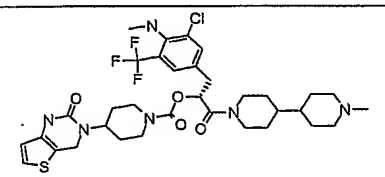
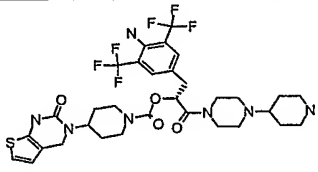
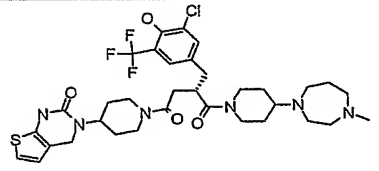
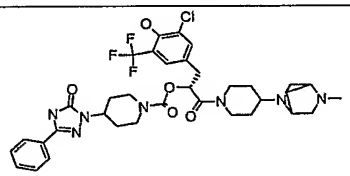
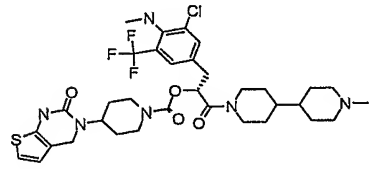
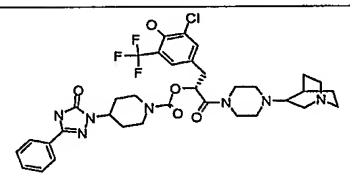
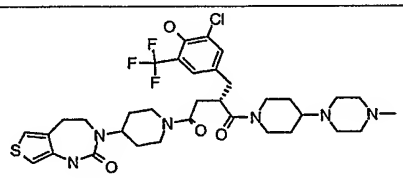
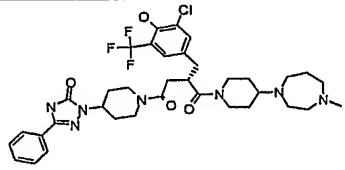
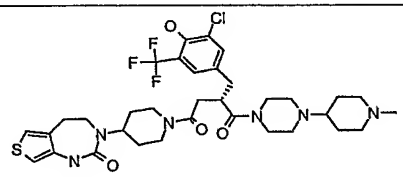
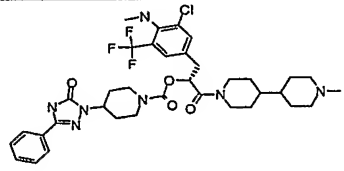
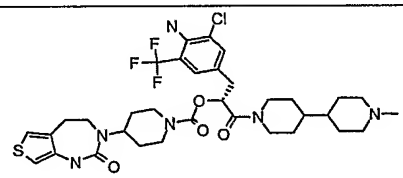
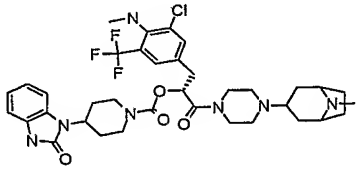
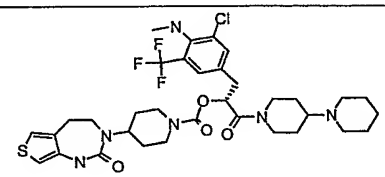
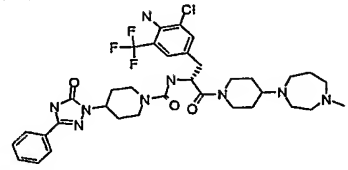
1511		1661	
1512		1662	
1513		1663	
1514		1664	
1515		1665	
1516		1666	
1517		1667	
1518		1668	
1519		1669	
1520		1670	

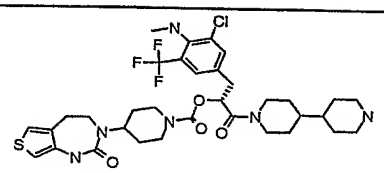
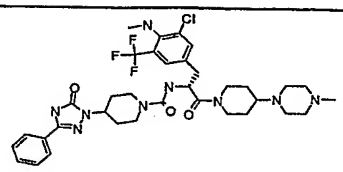
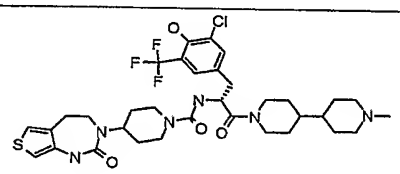
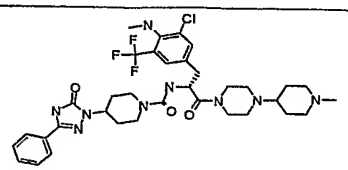
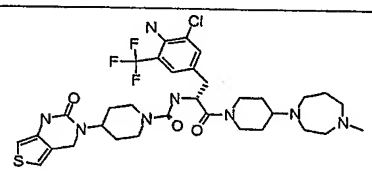
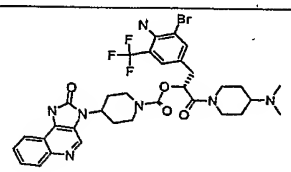
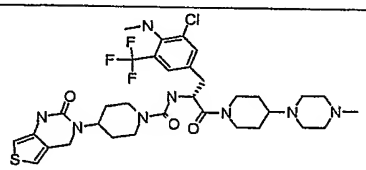
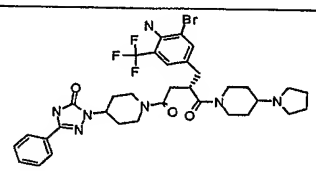
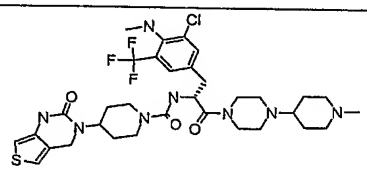
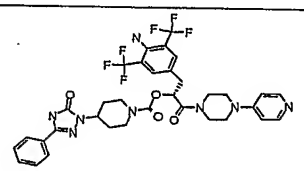
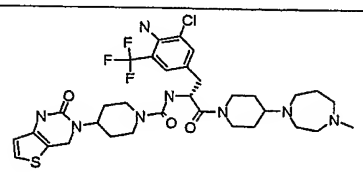
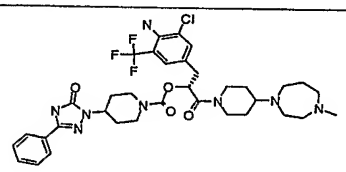
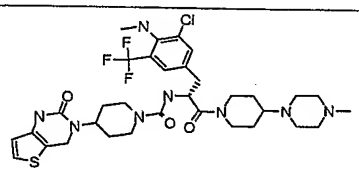
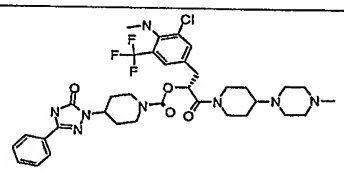
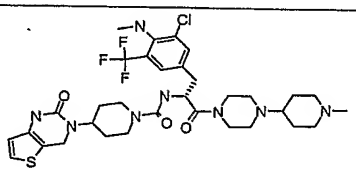
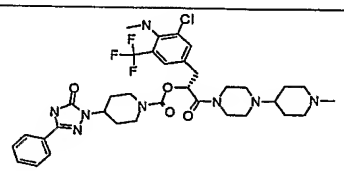
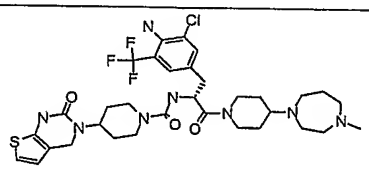
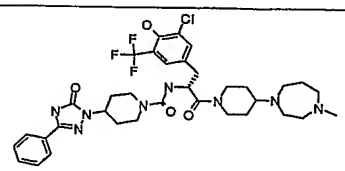
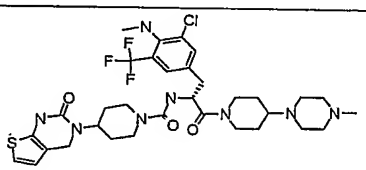
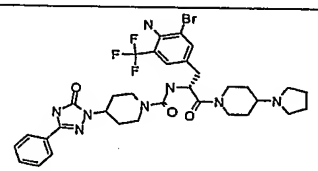
1521		1671	
1522		1672	
1523		1673	
1524		1674	
1525		1675	
1526		1676	
1527		1677	
1528		1678	
1529		1679	
1530		1680	

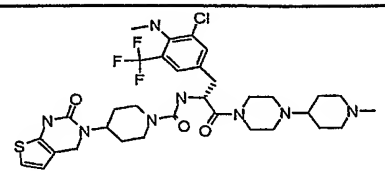
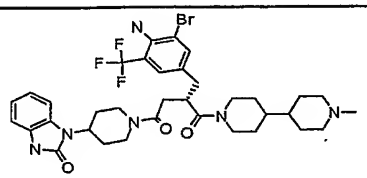
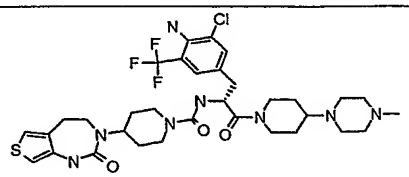
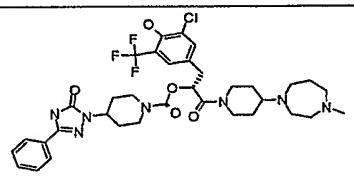
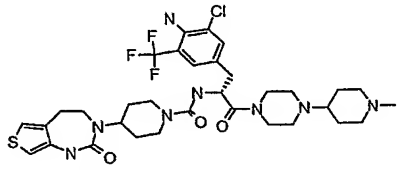
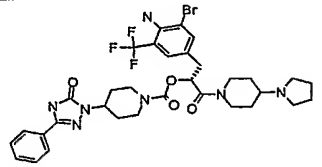
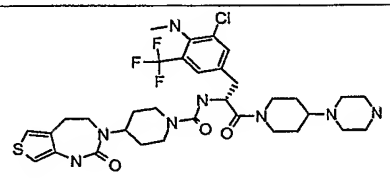
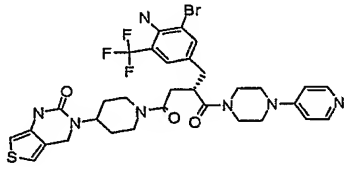
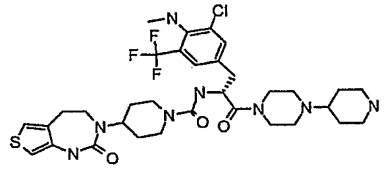
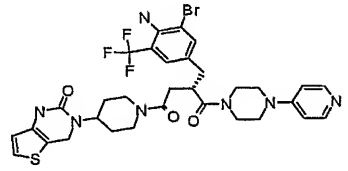
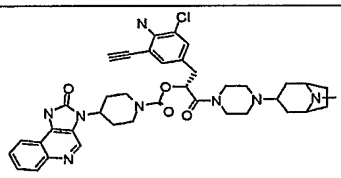
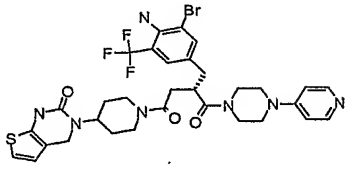
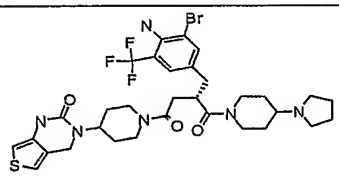
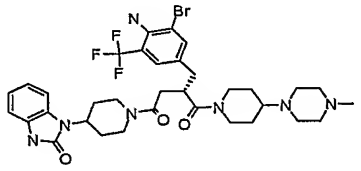
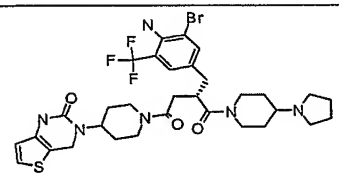
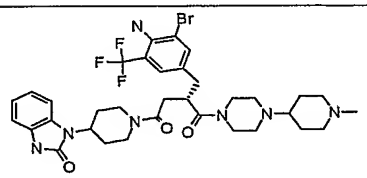
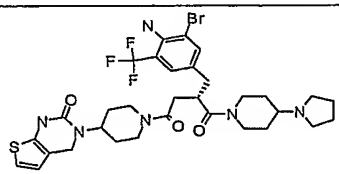
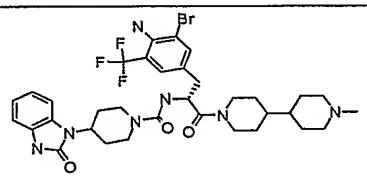
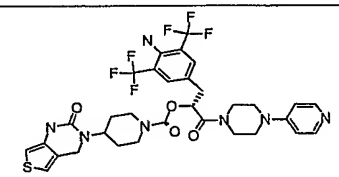
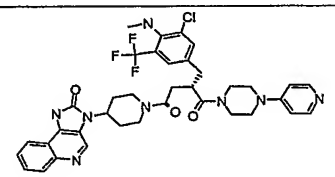
1531		1681	
1532		1682	
1533		1683	
1534		1684	
1535		1685	
1536		1686	
1537		1687	
1538		1688	
1539		1689	
1540		1690	

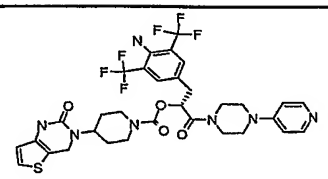
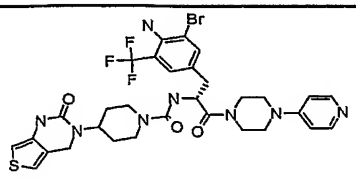
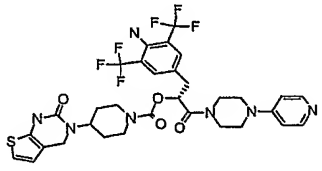
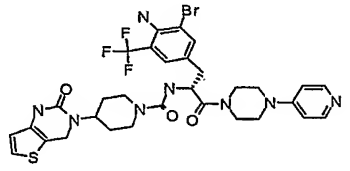
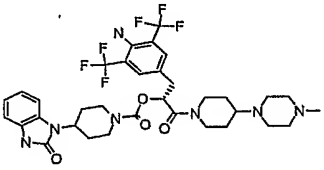
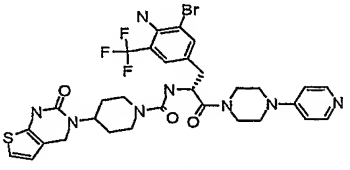
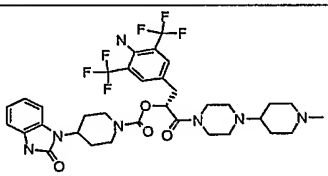
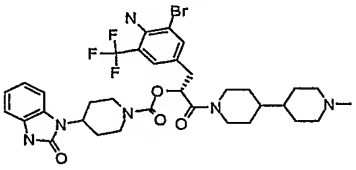
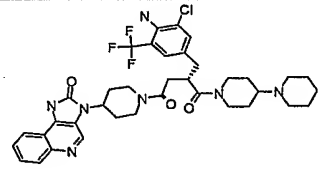
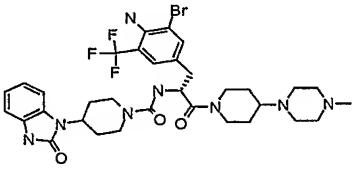
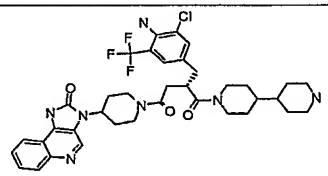
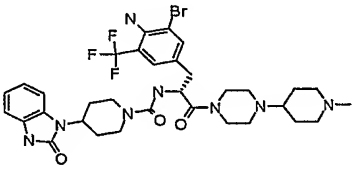
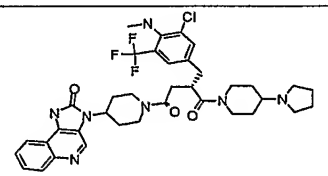
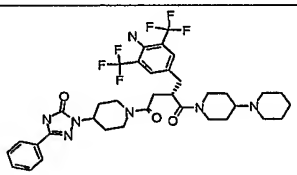
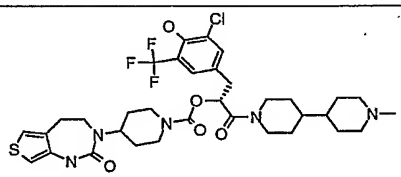
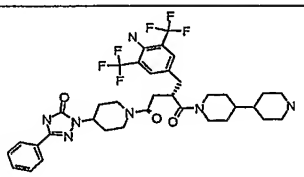
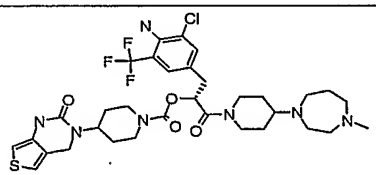
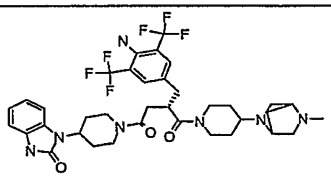
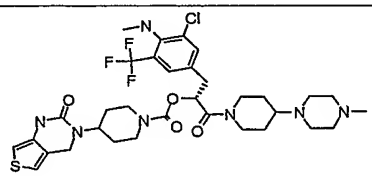
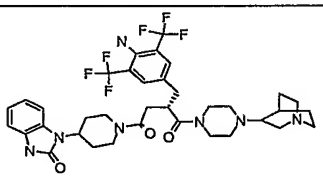
1541		1691	
1542		1692	
1543		1693	
1544		1694	
1545		1695	
1546		1696	
1547		1697	
1548		1698	
1549		1699	
1550		1700	

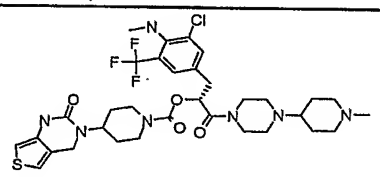
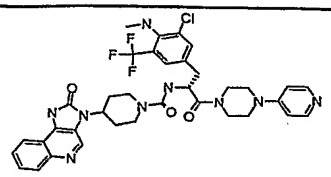
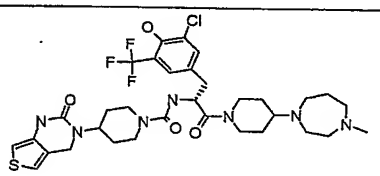
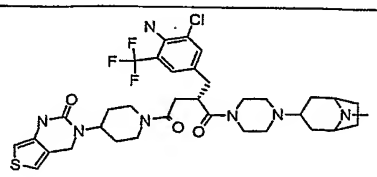
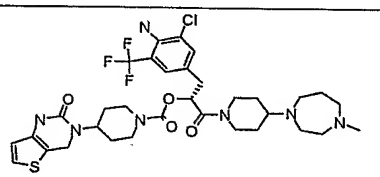
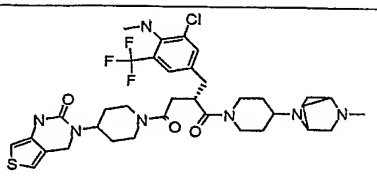
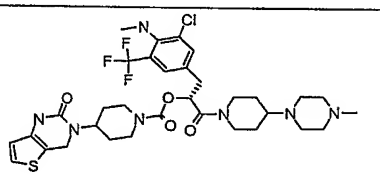
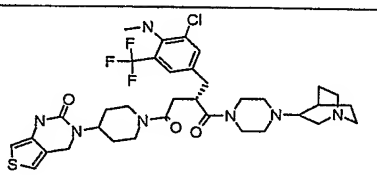
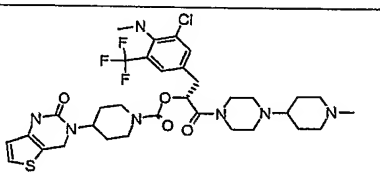
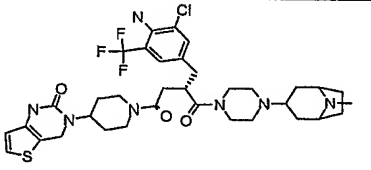
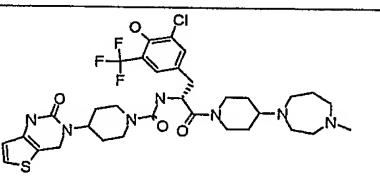
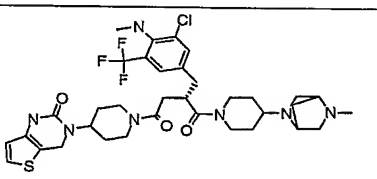
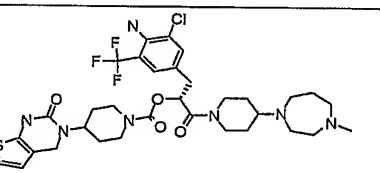
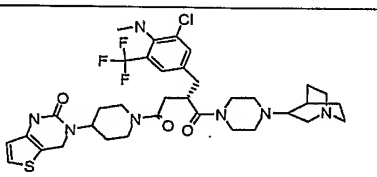
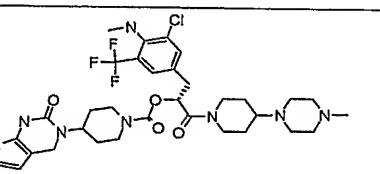
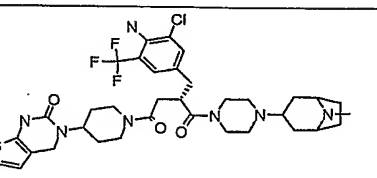
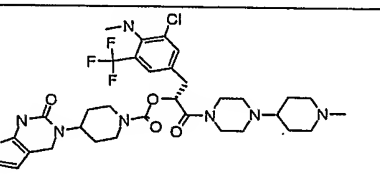
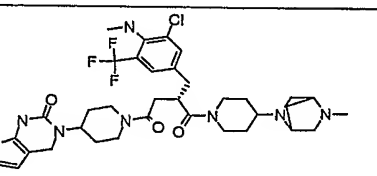
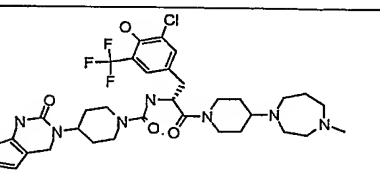
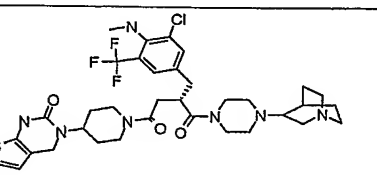
1551		1701	
1552		1702	
1553		1703	
1554		1704	
1555		1705	
1556		1706	
1557		1707	
1558		1708	
1559		1709	
1560		1710	

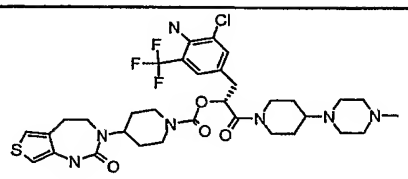
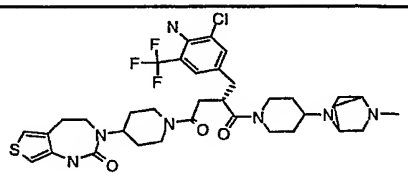
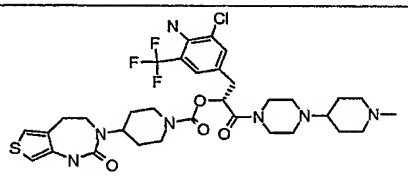
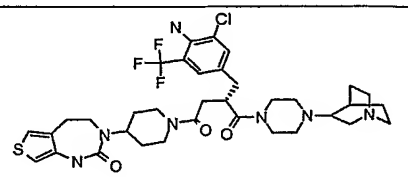
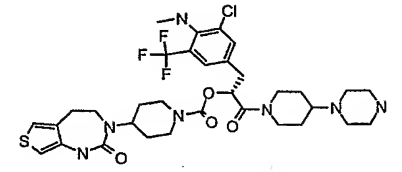
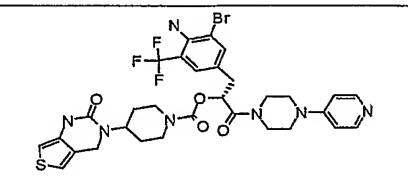
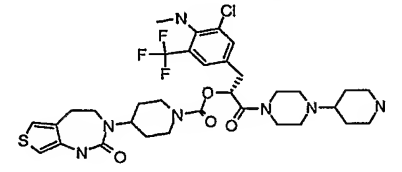
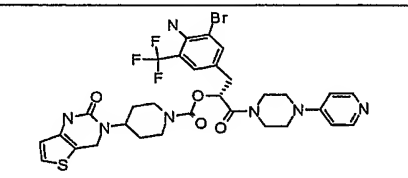
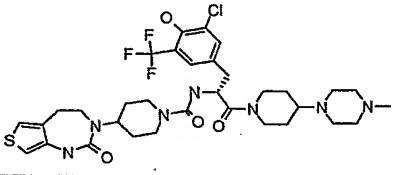
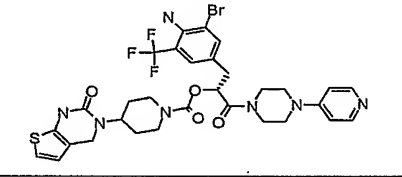
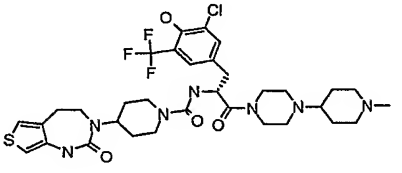
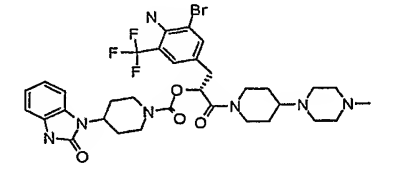
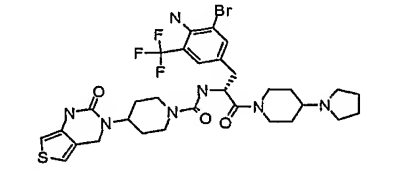
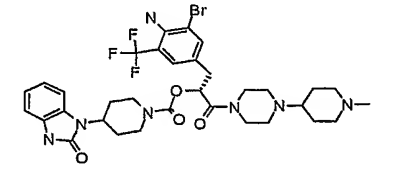
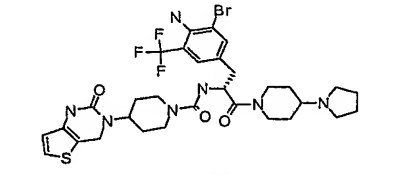
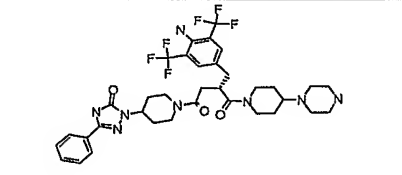
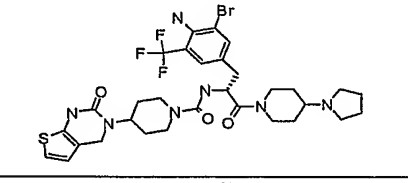
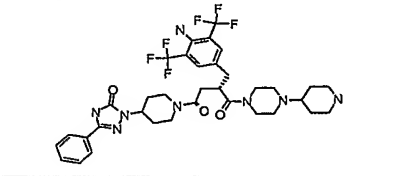
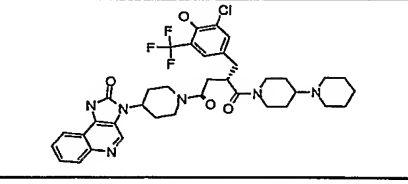
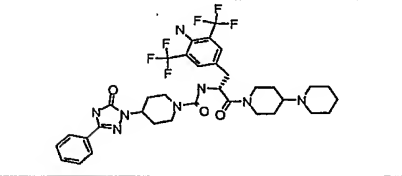
1561		1711	
1562		1712	
1563		1713	
1564		1714	
1565		1715	
1566		1716	
1567		1717	
1568		1718	
1569		1719	
1570		1720	

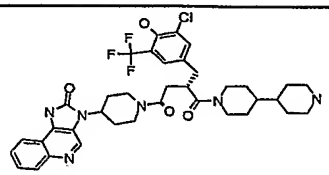
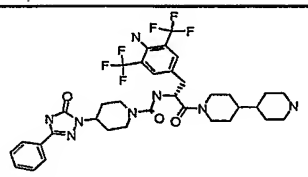
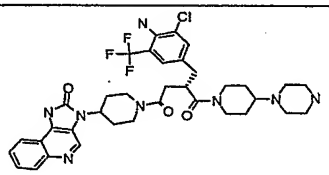
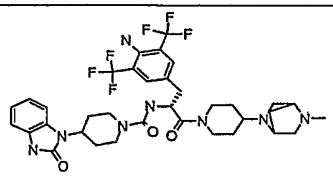
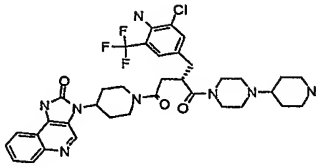
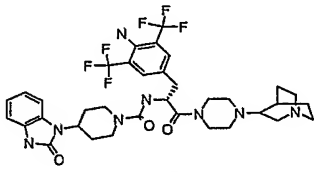
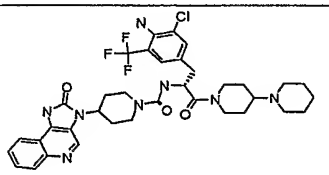
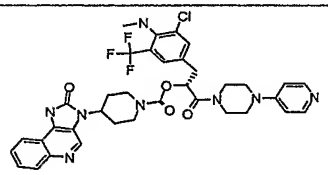
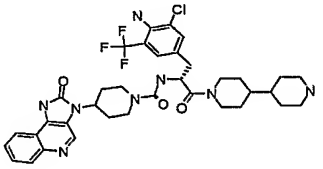
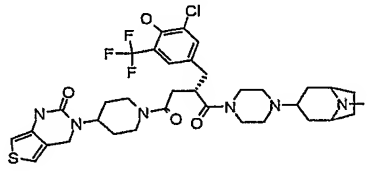
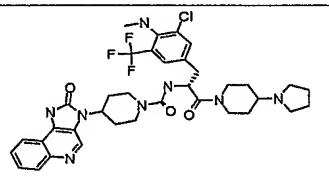
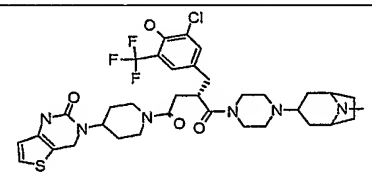
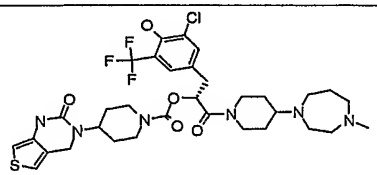
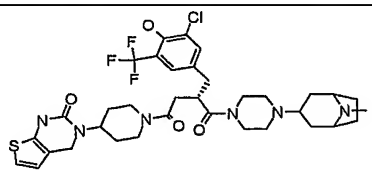
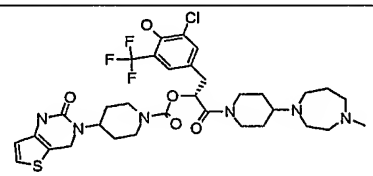
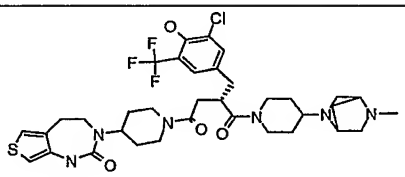
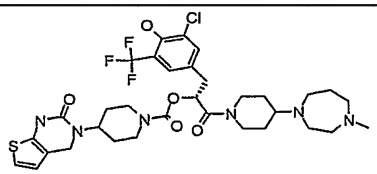
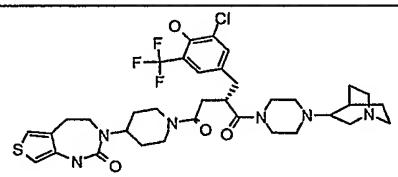
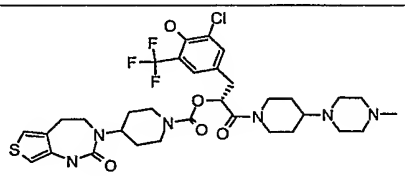
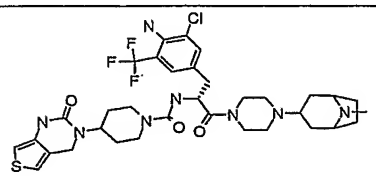
1571		1721		
1572		1722		
1573		1723		
1574		1724		
1575		1725		
1576		1726		
1577		1727		
1578		1728		
1579		1729		
1580		1730		

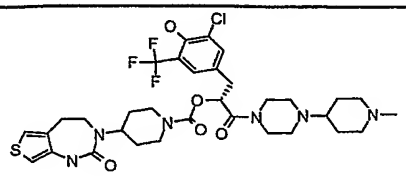
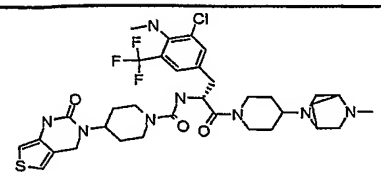
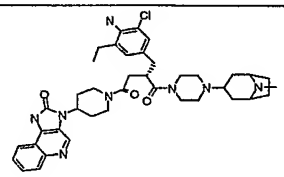
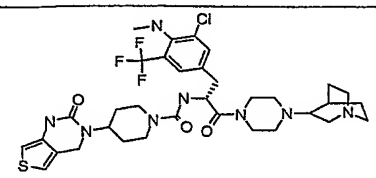
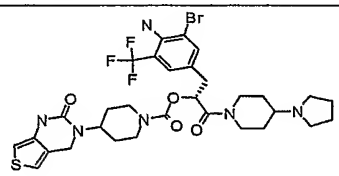
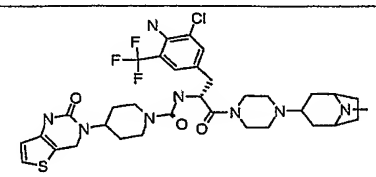
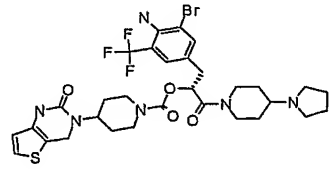
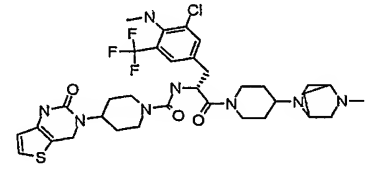
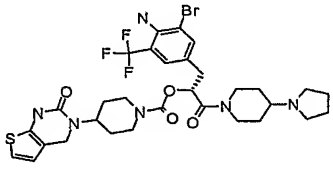
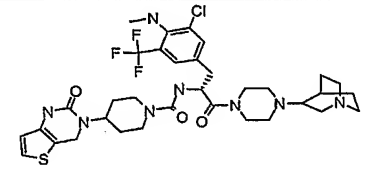
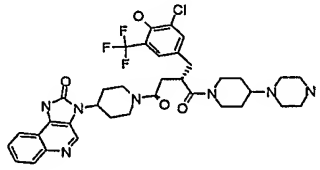
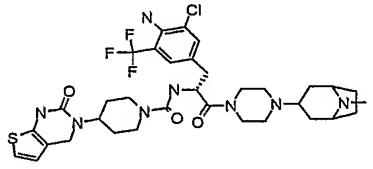
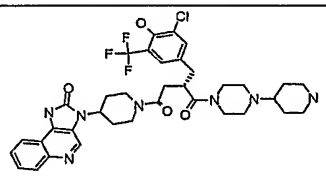
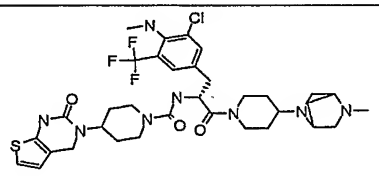
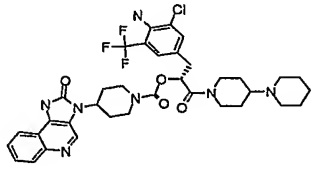
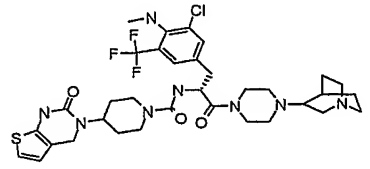
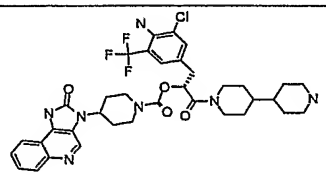
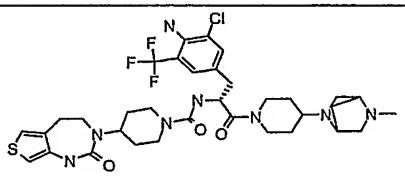
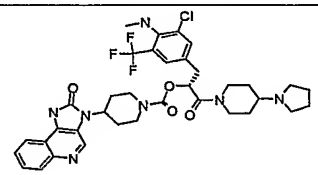
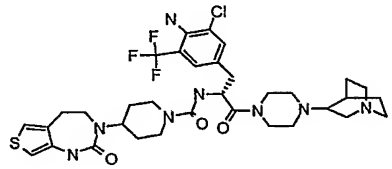
1581		1731	
1582		1732	
1583		1733	
1584		1734	
1585		1735	
1586		1736	
1587		1737	
1588		1738	
1589		1739	
1590		1740	

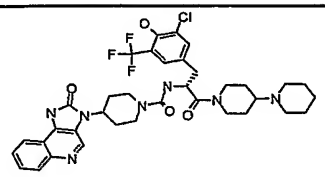
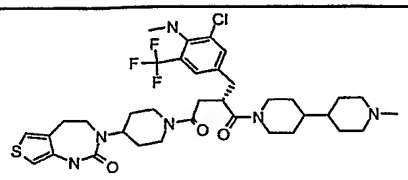
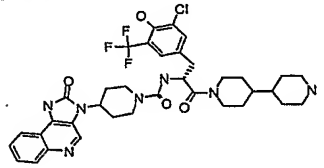
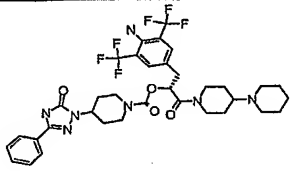
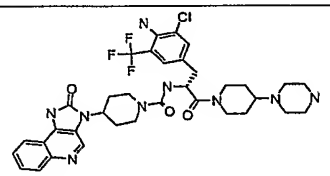
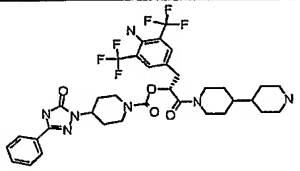
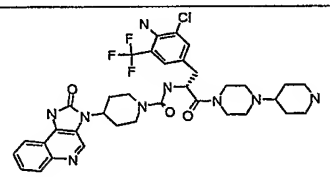
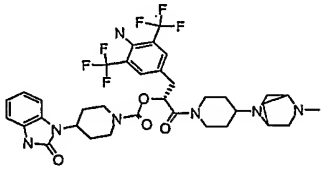
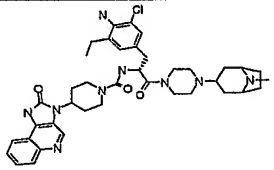
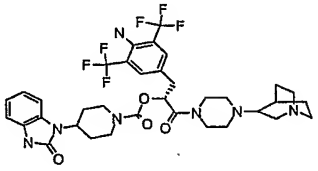
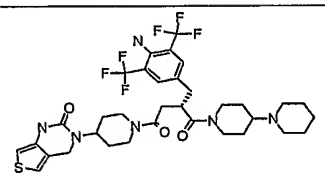
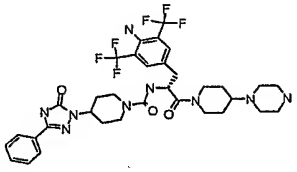
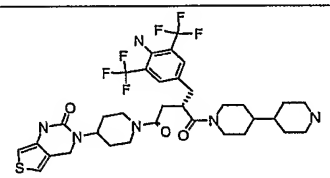
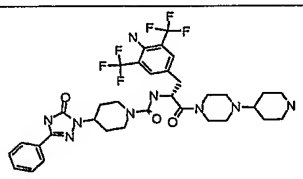
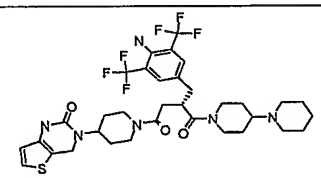
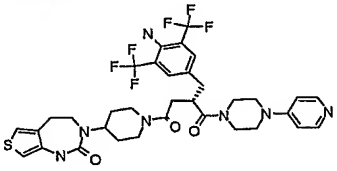
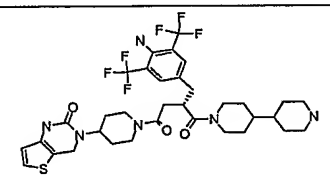
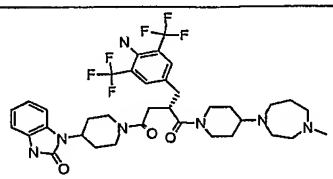
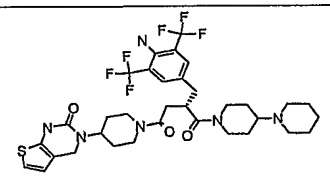
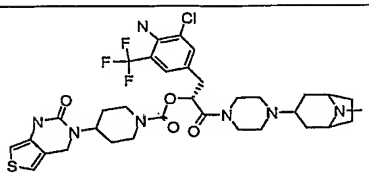
1591		1741	
1592		1742	
1593		1743	
1594		1744	
1595		1745	
1596		1746	
1597		1747	
1598		1748	
1599		1749	
1600		1750	

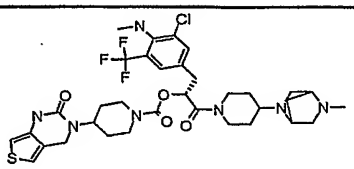
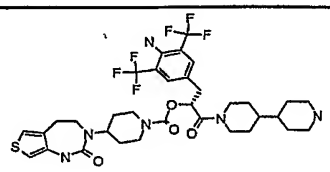
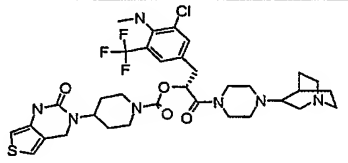
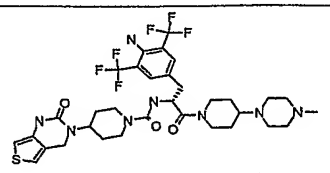
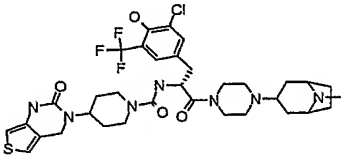
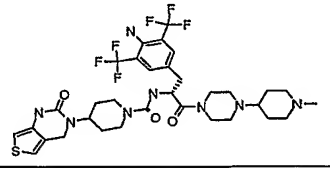
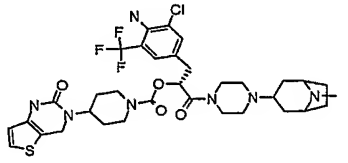
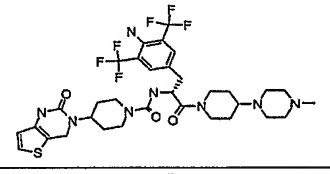
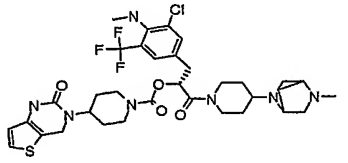
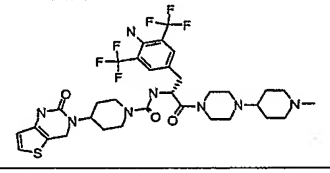
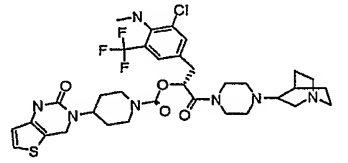
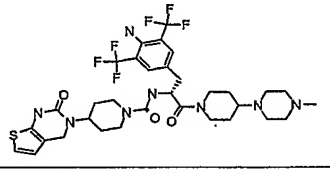
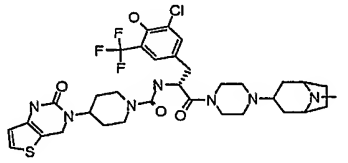
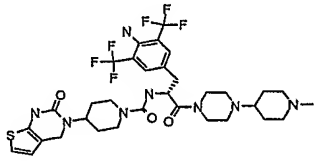
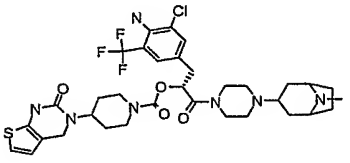
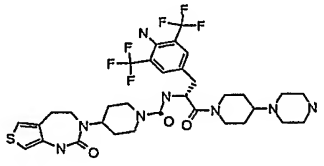
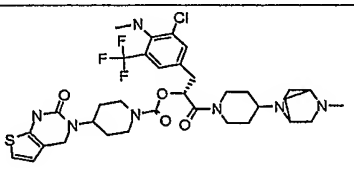
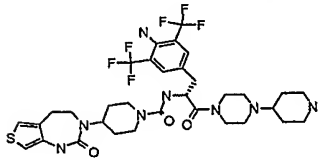
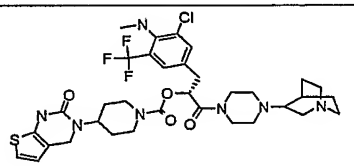
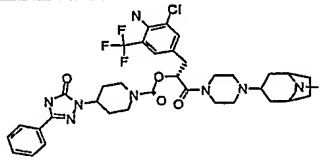
1601		1751	
1602		1752	
1603		1753	
1604		1754	
1605		1755	
1606		1756	
1607		1757	
1608		1758	
1609		1759	
1610		1760	

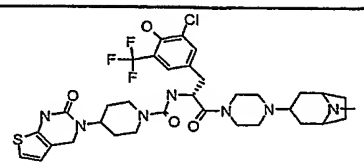
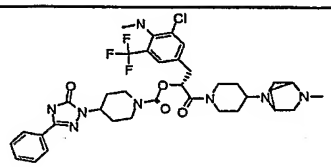
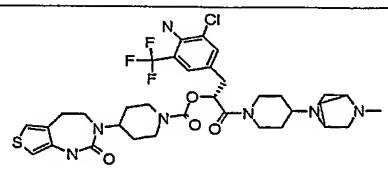
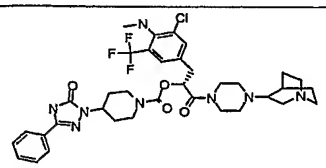
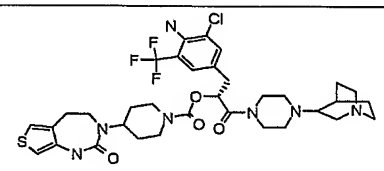
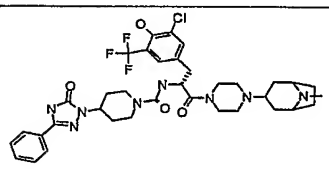
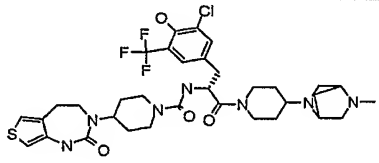
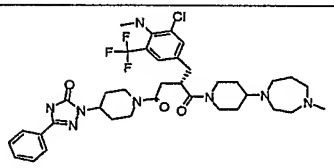
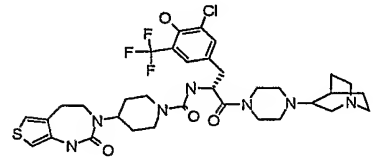
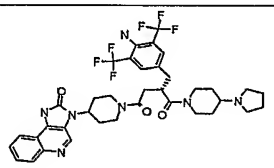
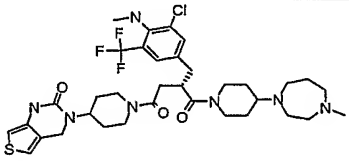
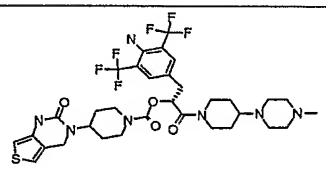
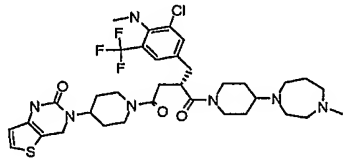
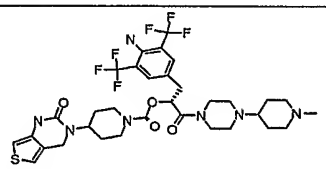
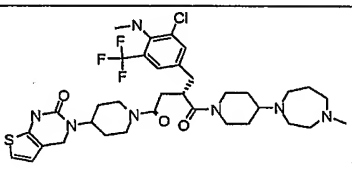
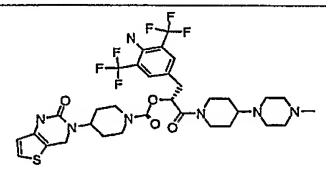
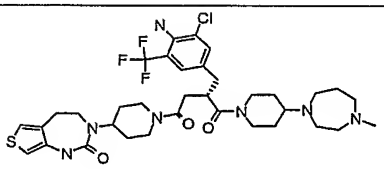
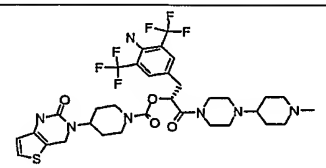
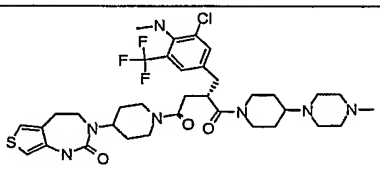
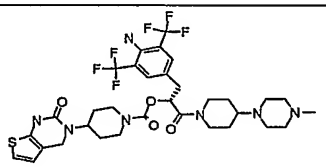
1611		1761	
1612		1762	
1613		1763	
1614		1764	
1615		1765	
1616		1766	
1617		1767	
1618		1768	
1619		1769	
1620		1770	

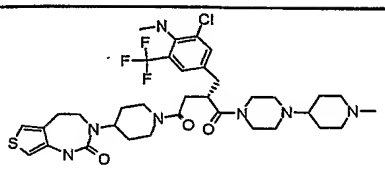
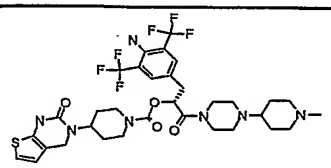
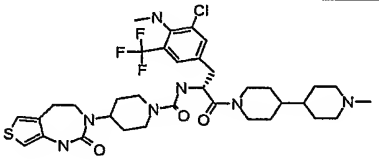
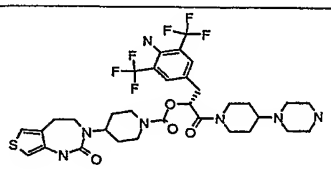
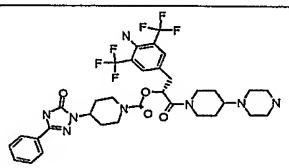
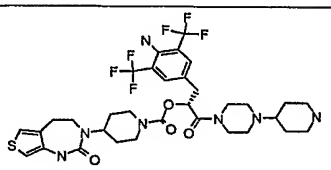
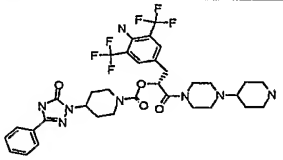
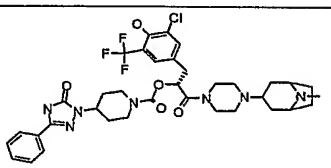
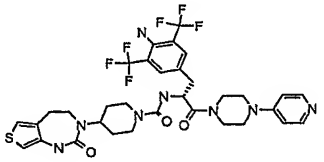
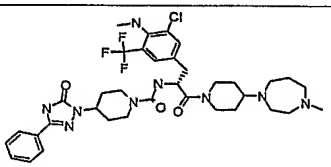
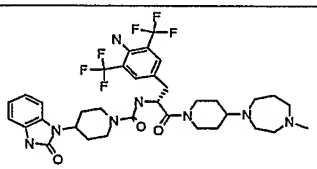
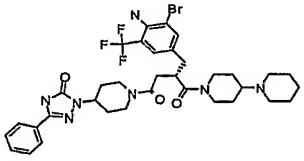
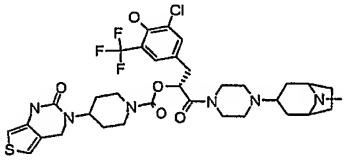
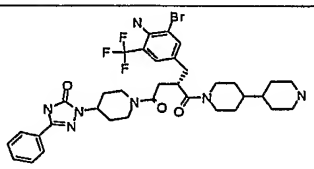
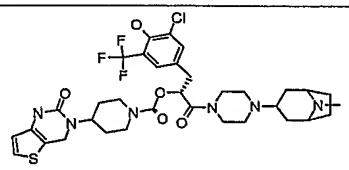
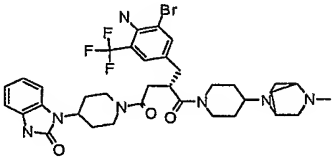
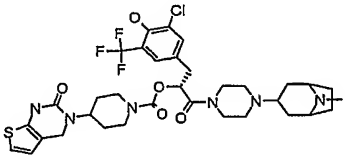
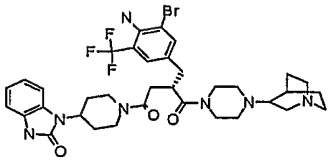
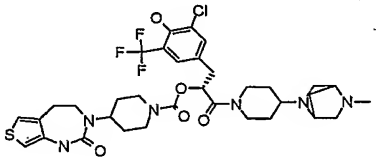
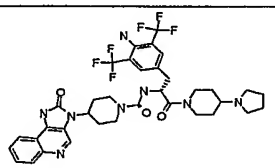
1621		1771	
1622		1772	
1623		1773	
1624		1774	
1625		1775	
1626		1776	
1627		1777	
1628		1778	
1629		1779	
1630		1780	

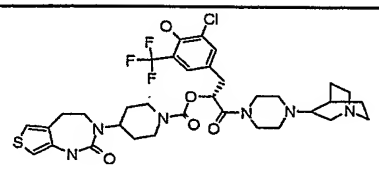
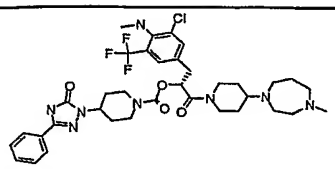
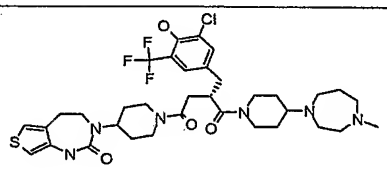
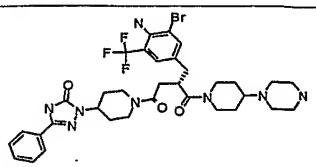
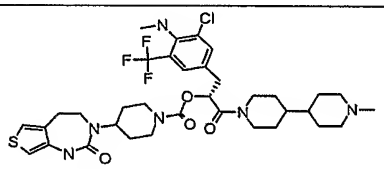
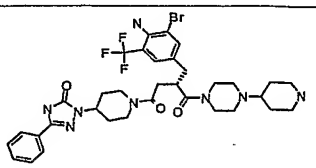
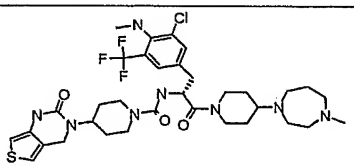
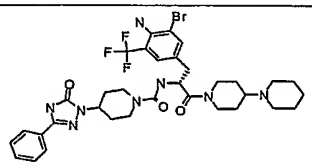
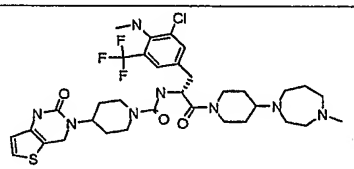
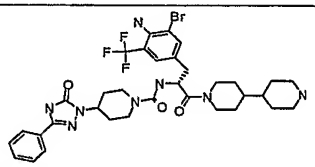
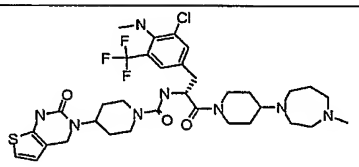
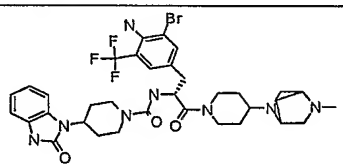
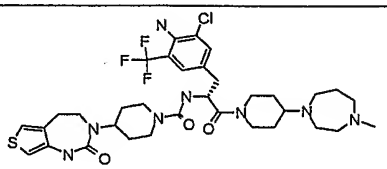
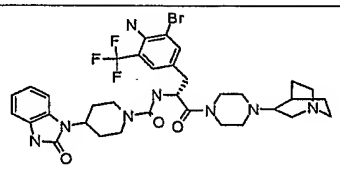
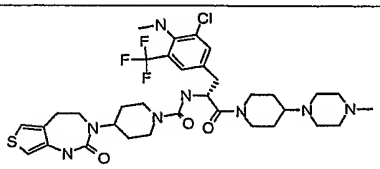
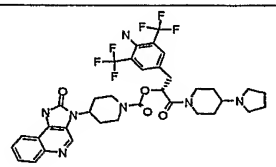
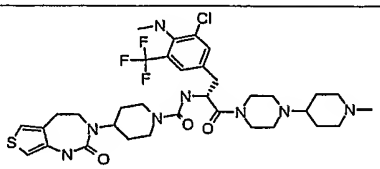
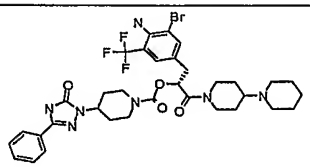
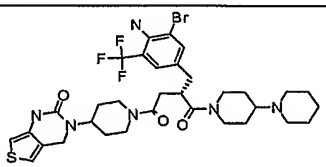
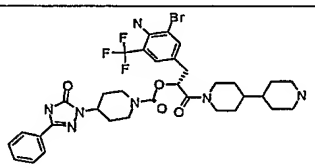
1631		1781	
1632		1782	
1633		1783	
1634		1784	
1635		1785	
1636		1786	
1637		1787	
1638		1788	
1639		1789	
1640		1790	

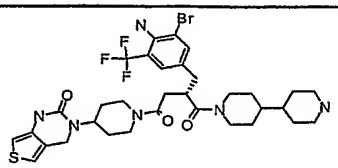
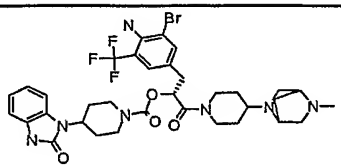
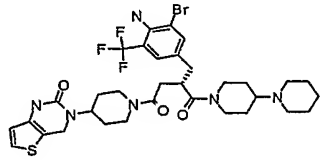
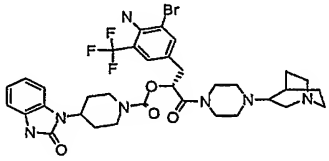
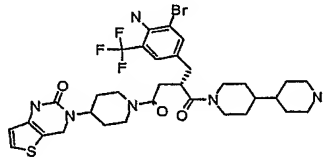
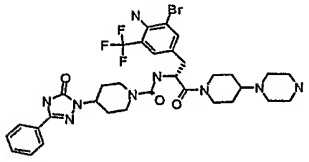
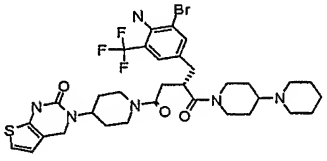
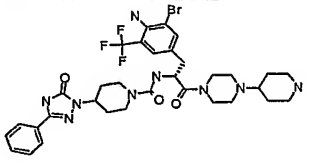
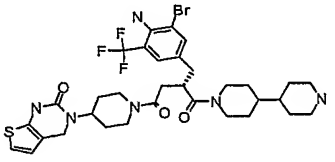
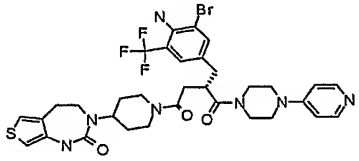
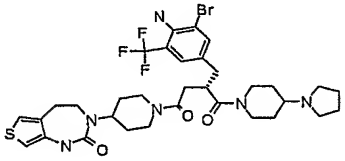
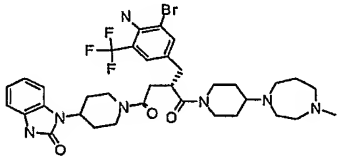
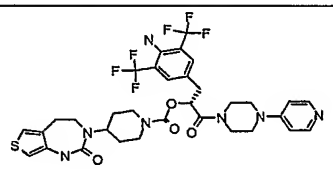
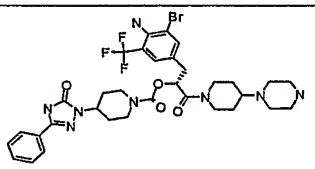
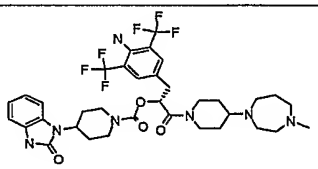
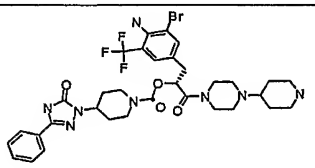
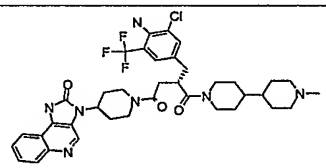
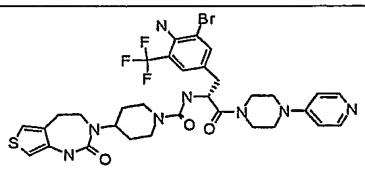
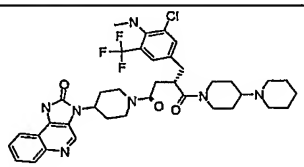
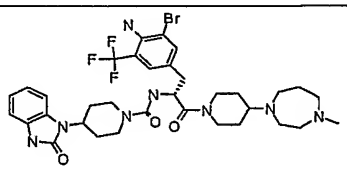
1641		1791	
1642		1792	
1643		1793	
1644		1794	
1645		1795	
1646		1796	
1647		1797	
1648		1798	
1649		1799	
1650		1800	

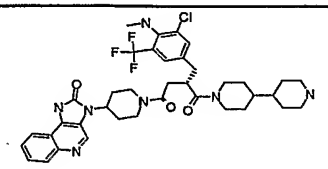
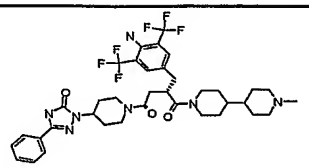
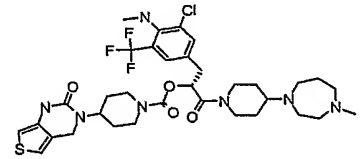
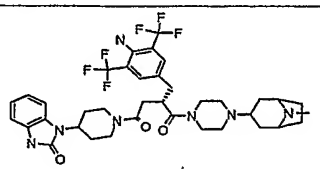
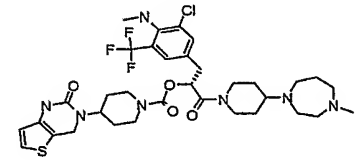
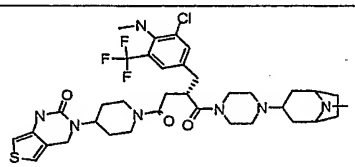
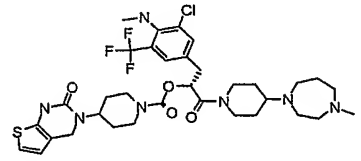
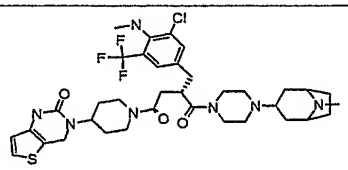
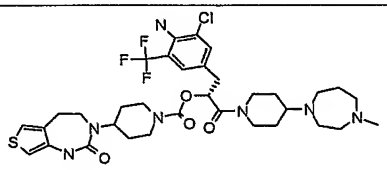
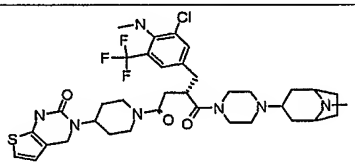
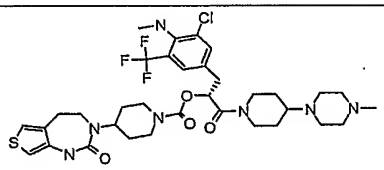
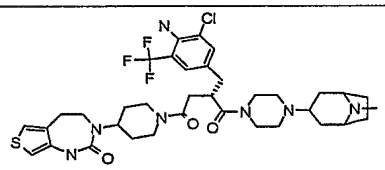
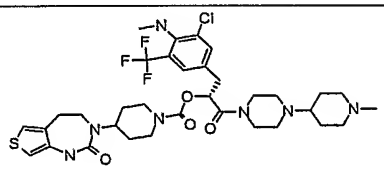
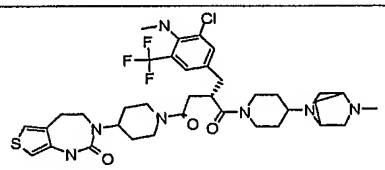
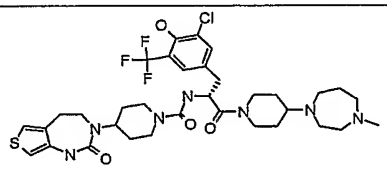
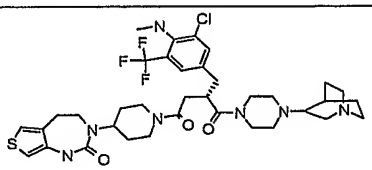
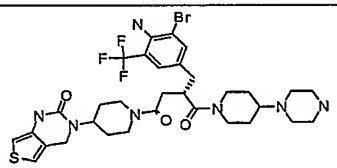
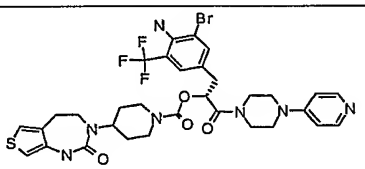
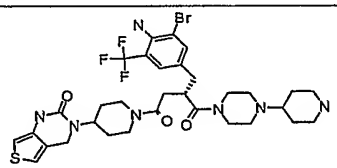
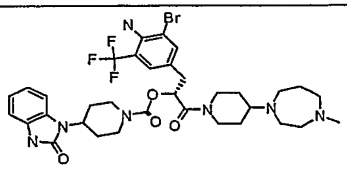
1801		1951	
1802		1952	
1803		1953	
1804		1954	
1805		1955	
1806		1956	
1807		1957	
1808		1958	
1809		1959	
1810		1960	

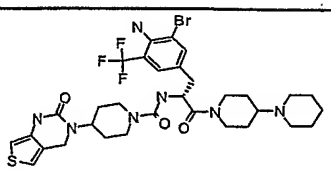
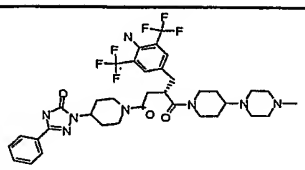
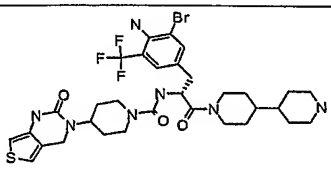
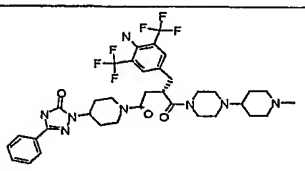
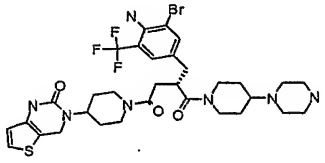
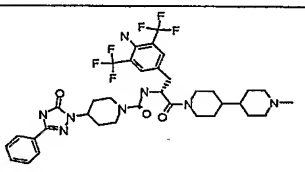
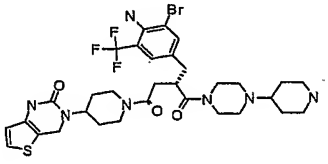
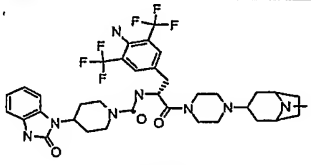
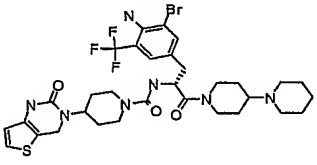
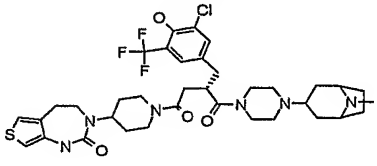
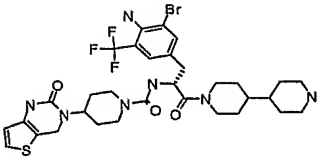
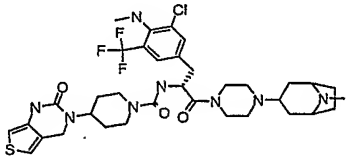
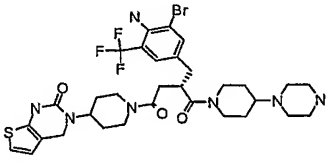
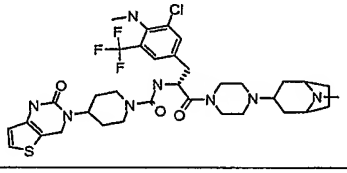
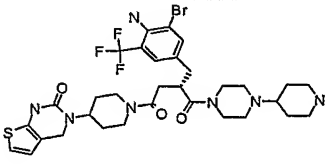
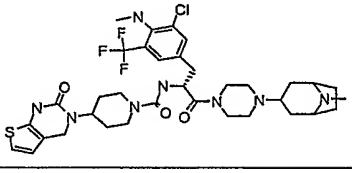
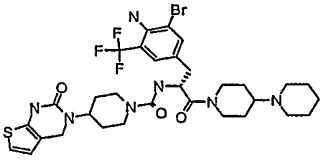
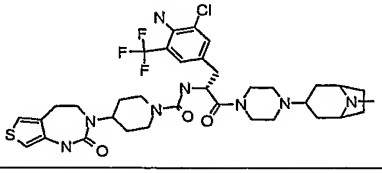
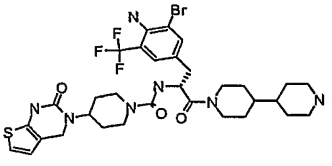
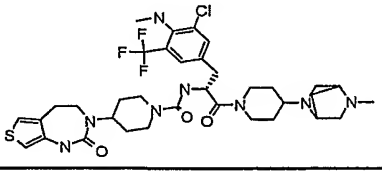
1811		1961	
1812		1962	
1813		1963	
1814		1964	
1815		1965	
1816		1966	
1817		1967	
1818		1968	
1819		1969	
1820		1970	

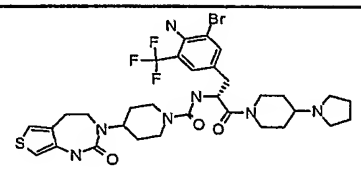
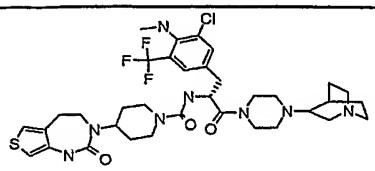
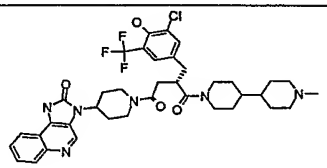
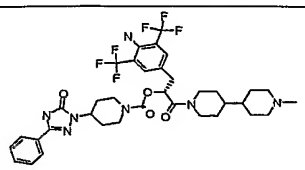
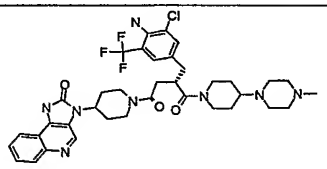
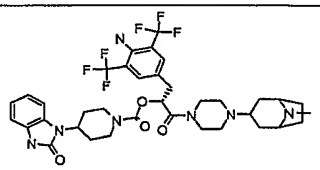
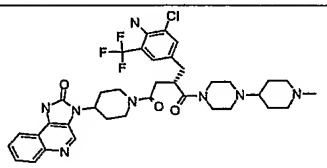
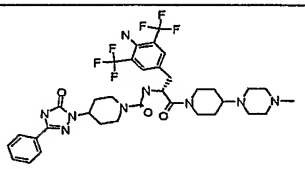
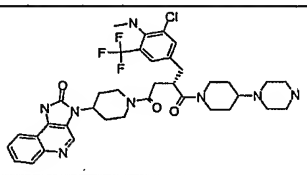
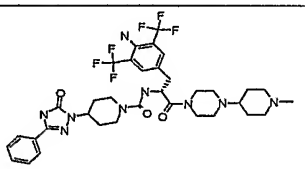
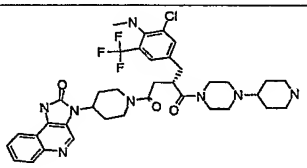
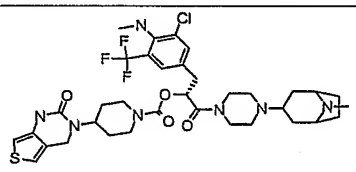
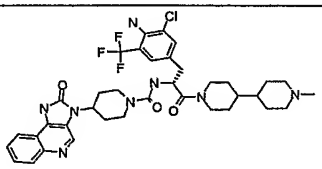
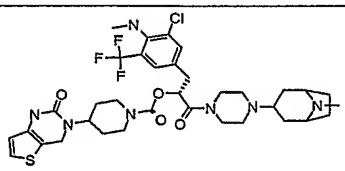
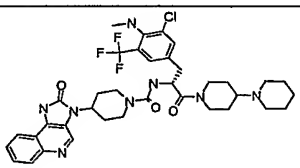
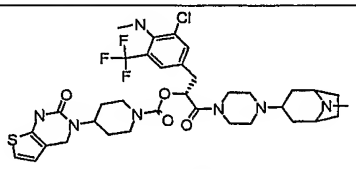
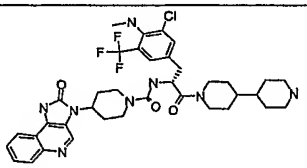
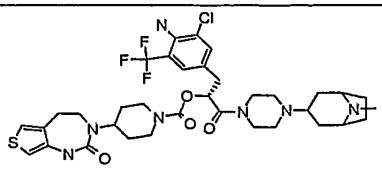
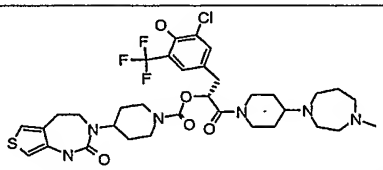
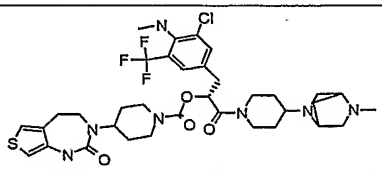
1821		1971	
1822		1972	
1823		1973	
1824		1974	
1825		1975	
1826		1976	
1827		1977	
1828		1978	
1829		1979	
1830		1980	

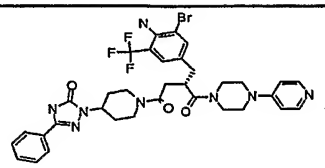
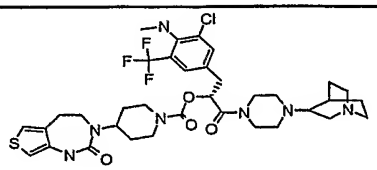
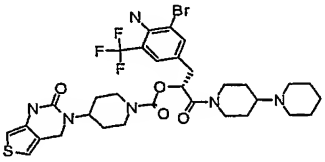
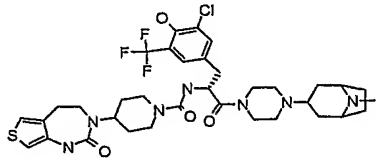
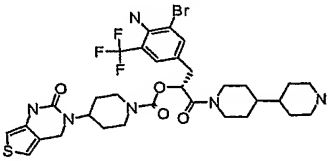
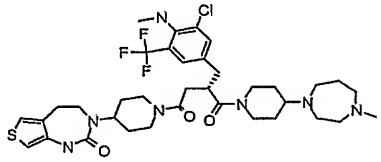
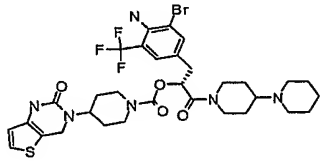
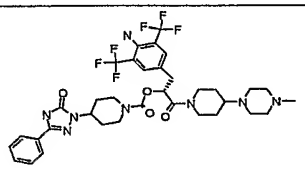
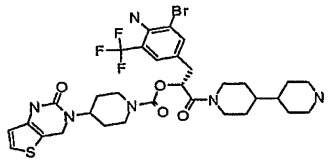
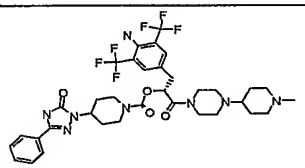
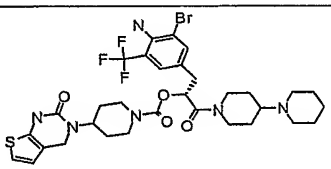
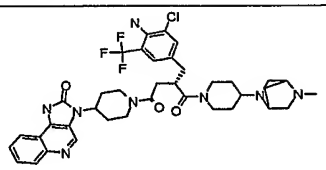
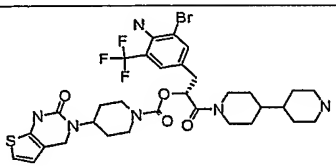
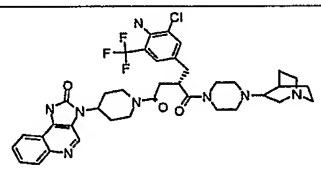
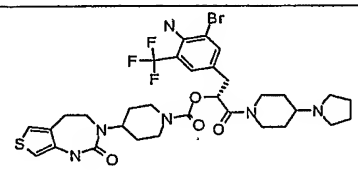
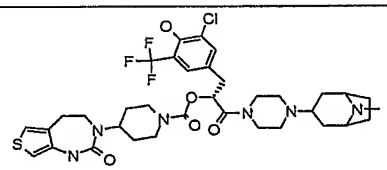
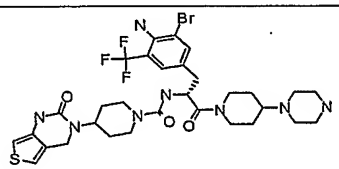
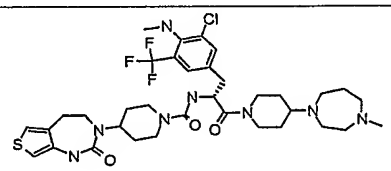
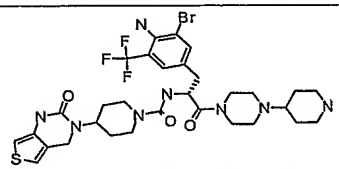
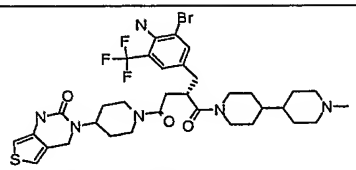
1831		1981	
1832		1982	
1833		1983	
1834		1984	
1835		1985	
1836		1986	
1837		1987	
1838		1988	
1839		1989	
1840		1990	

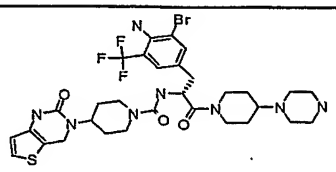
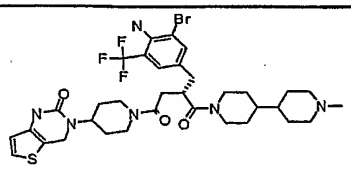
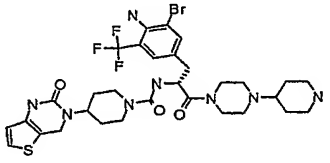
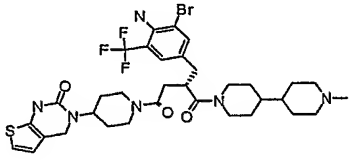
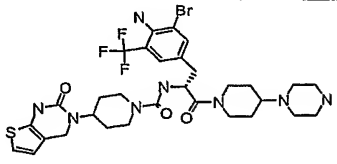
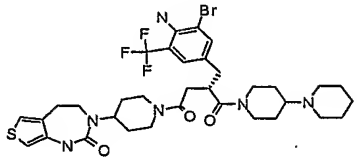
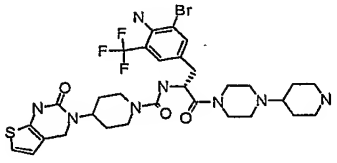
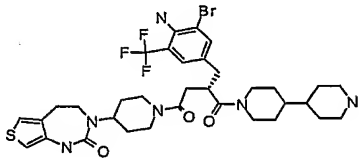
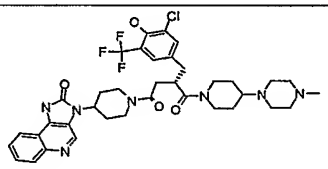
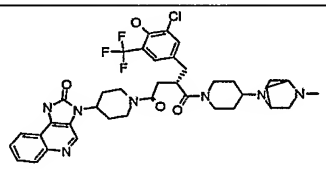
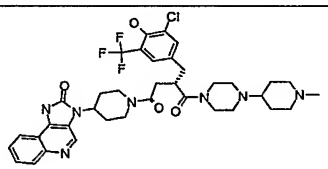
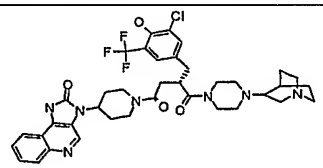
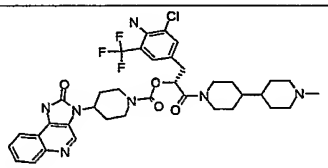
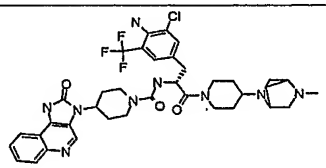
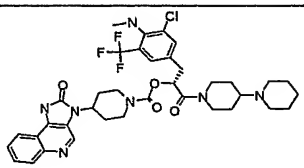
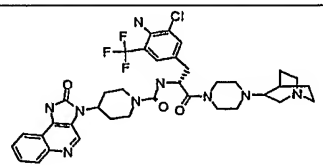
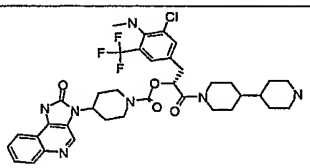
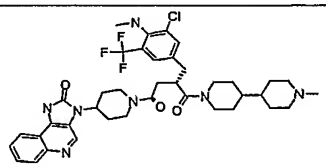
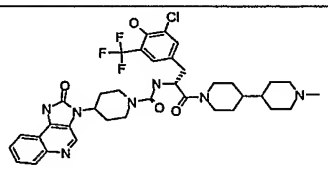
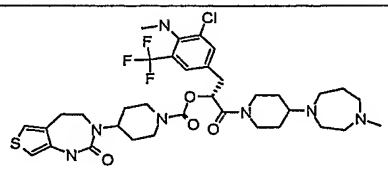
1841		1991	
1842		1992	
1843		1993	
1844		1994	
1845		1995	
1846		1996	
1847		1997	
1848		1998	
1849		1999	
1850		2000	

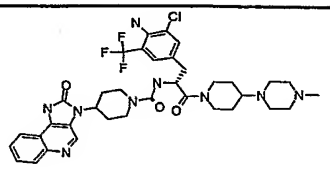
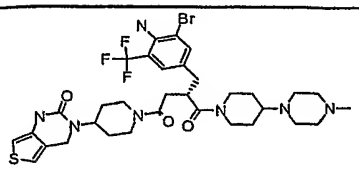
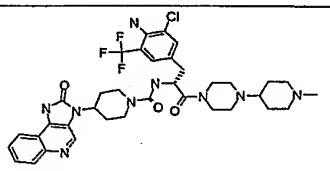
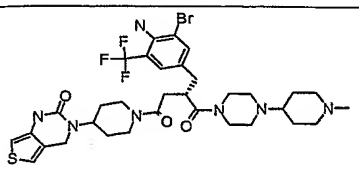
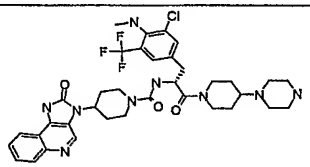
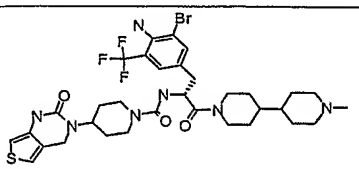
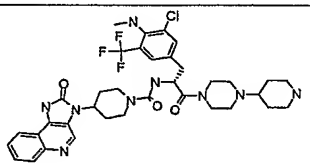
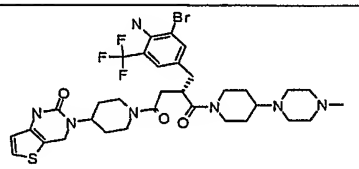
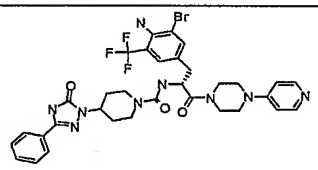
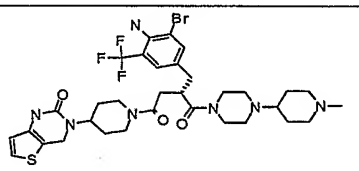
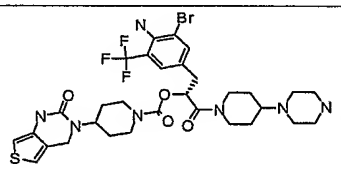
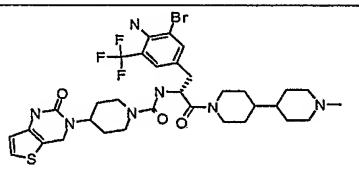
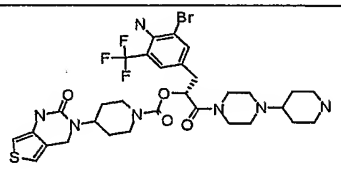
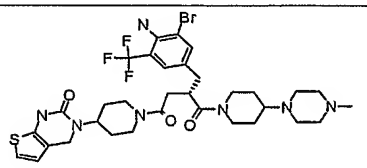
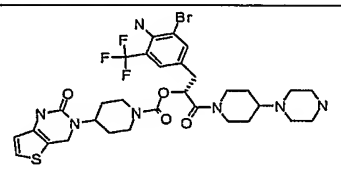
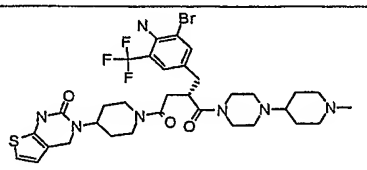
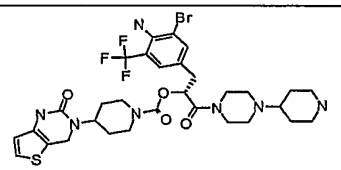
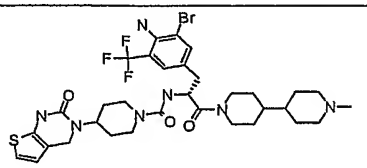
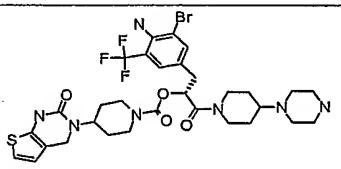
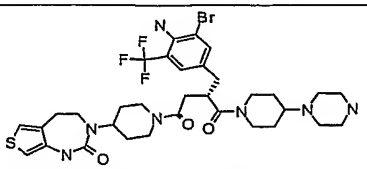
1851		2001	
1852		2002	
1853		2003	
1854		2004	
1855		2005	
1856		2006	
1857		2007	
1858		2008	
1859		2009	
1860		2010	

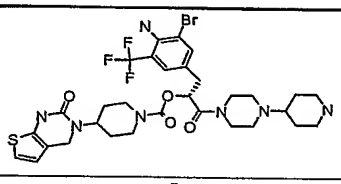
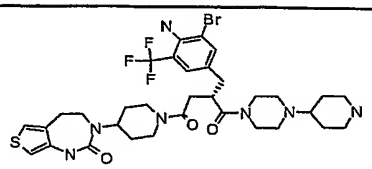
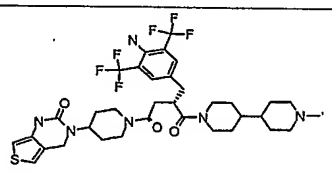
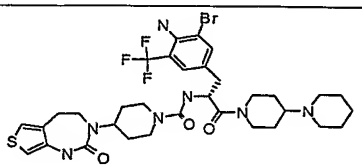
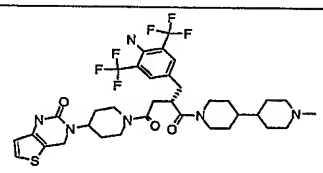
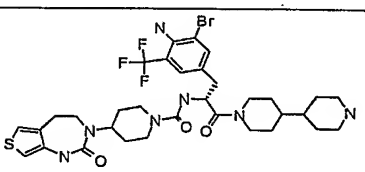
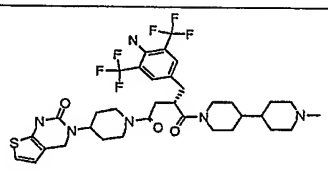
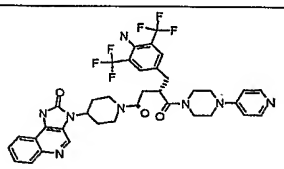
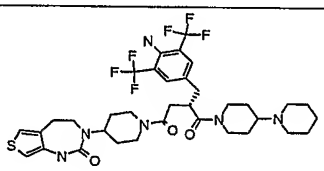
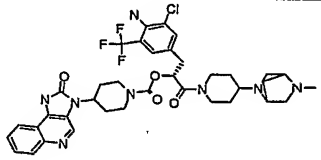
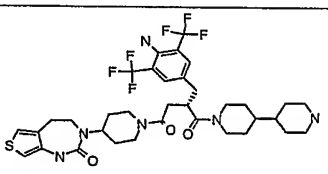
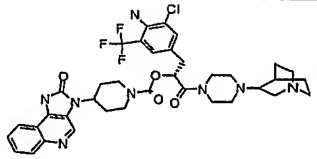
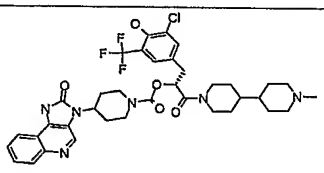
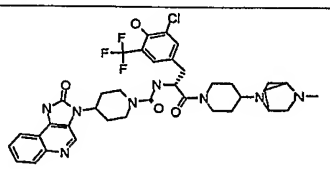
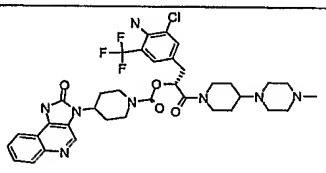
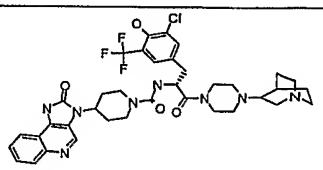
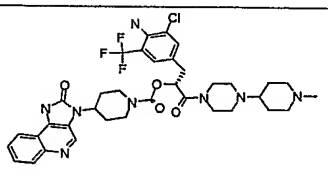
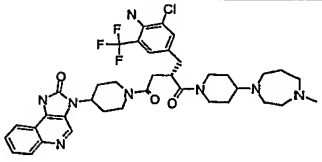
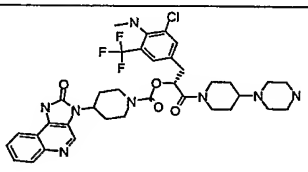
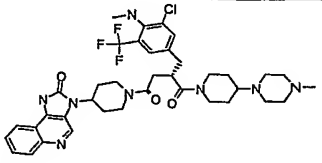
1861		2011	
1862		2012	
1863		2013	
1864		2014	
1865		2015	
1866		2016	
1867		2017	
1868		2018	
1869		2019	
1870		2020	

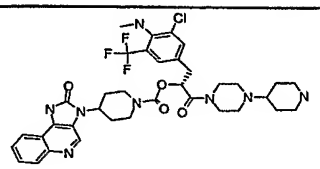
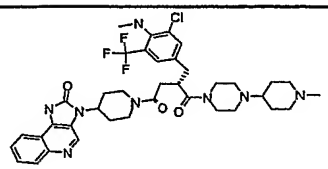
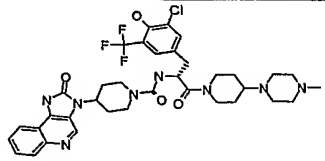
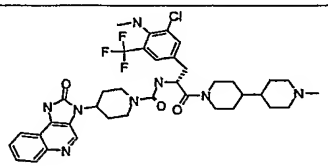
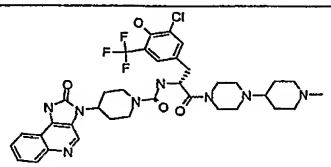
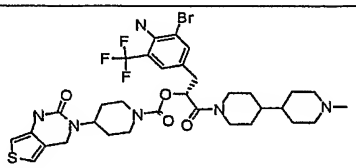
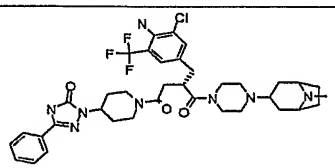
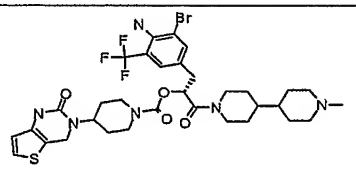
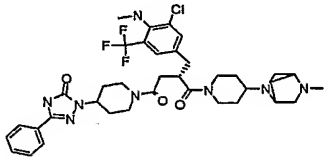
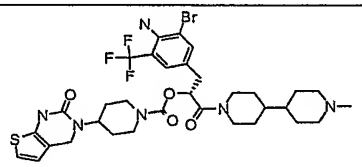
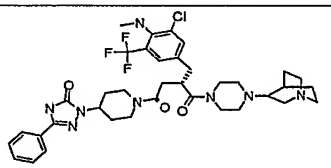
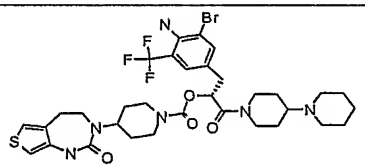
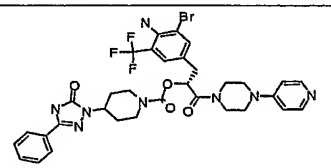
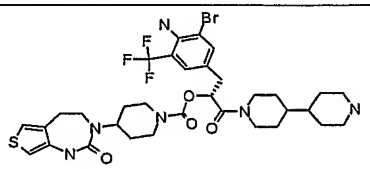
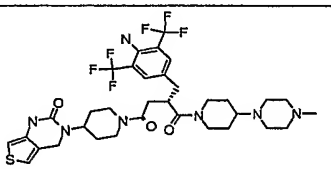
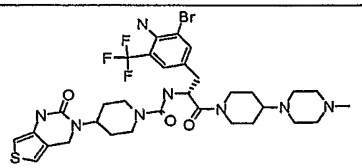
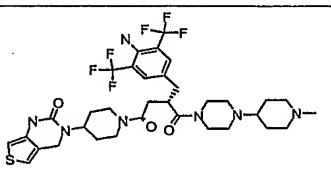
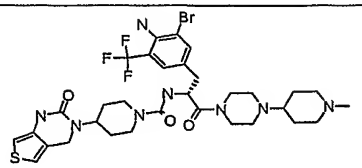
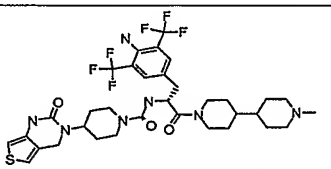
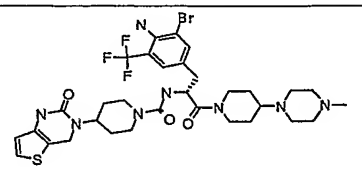
1871		2021	
1872		2022	
1873		2023	
1874		2024	
1875		2025	
1876		2026	
1877		2027	
1878		2028	
1879		2029	
1880		2030	

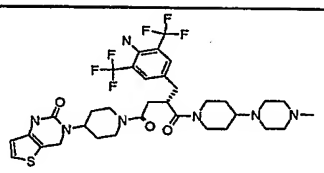
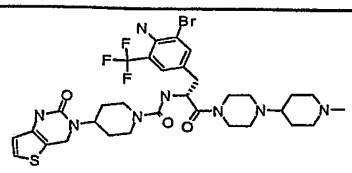
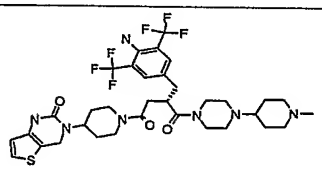
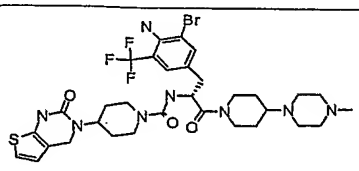
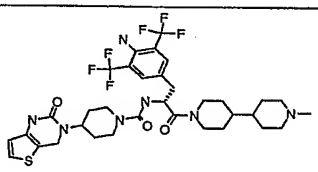
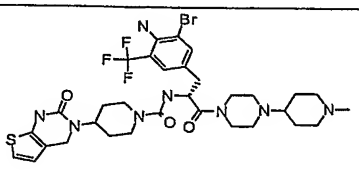
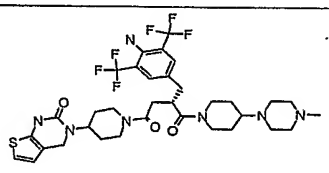
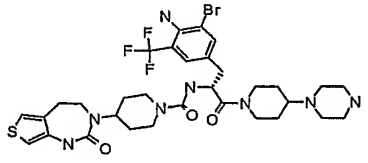
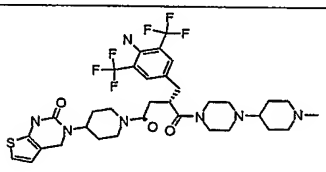
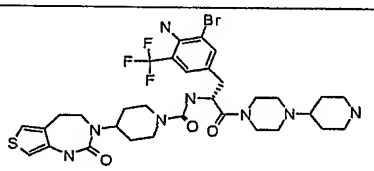
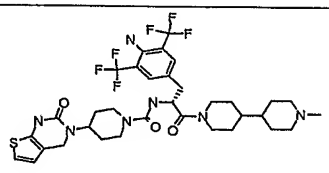
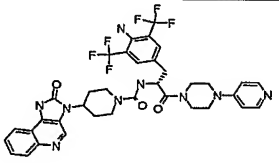
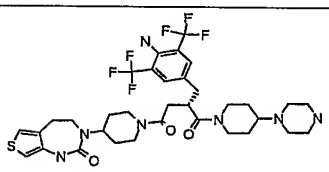
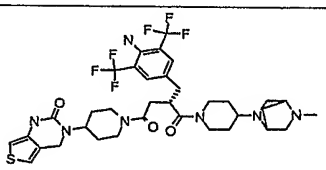
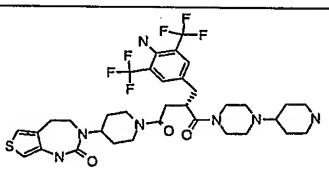
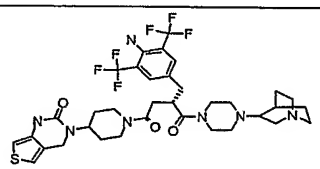
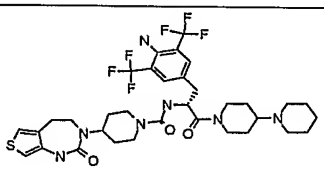
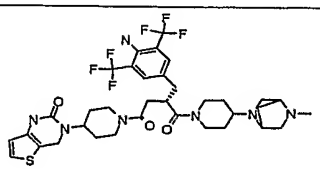
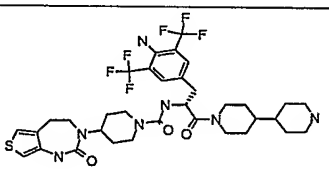
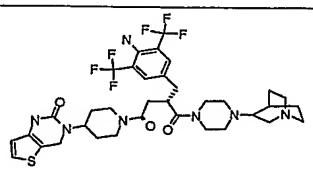
1881		2031	
1882		2032	
1883		2033	
1884		2034	
1885		2035	
1886		2036	
1887		2037	
1888		2038	
1889		2039	
1890		2040	

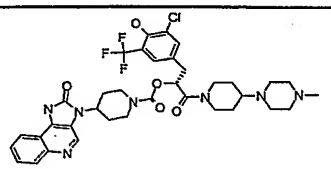
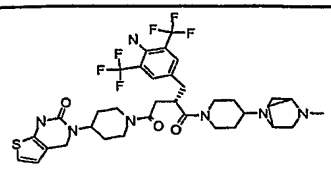
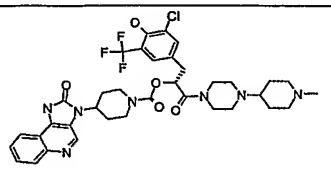
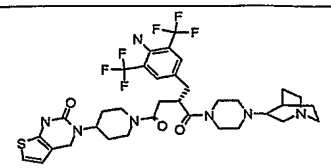
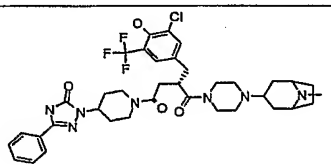
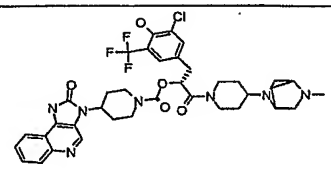
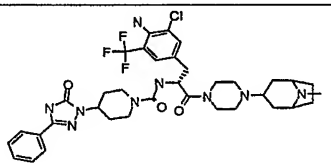
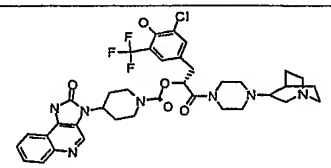
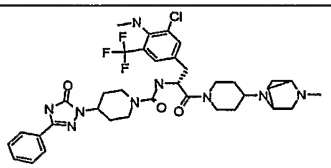
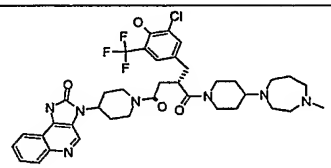
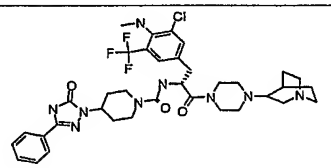
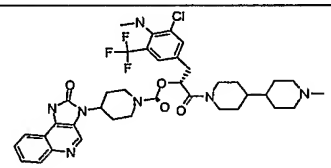
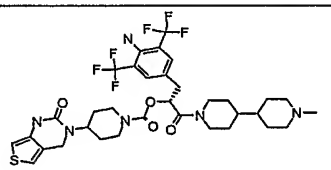
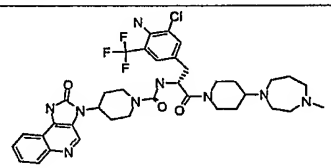
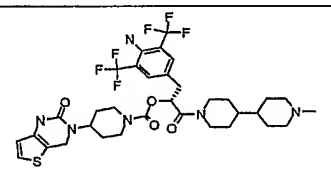
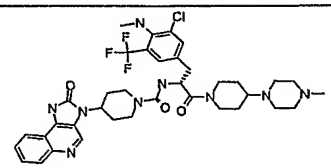
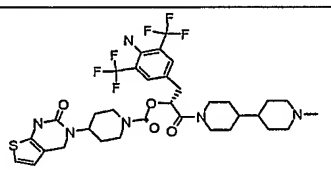
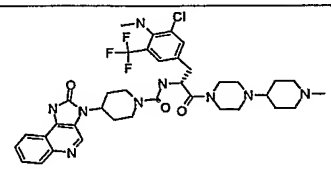
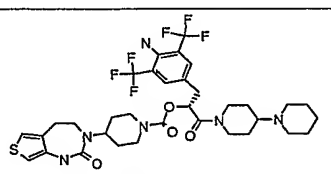
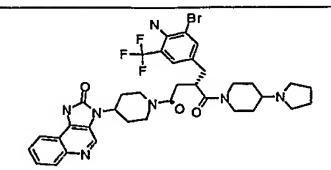
1891		2041	
1892		2042	
1893		2043	
1894		2044	
1895		2045	
1896		2046	
1897		2047	
1898		2048	
1899		2049	
1900		2050	

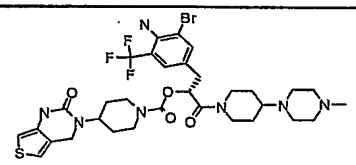
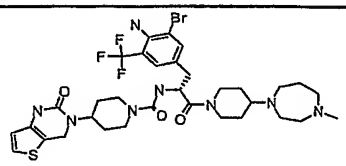
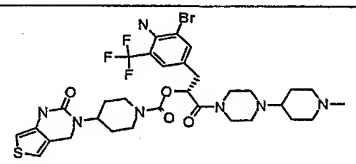
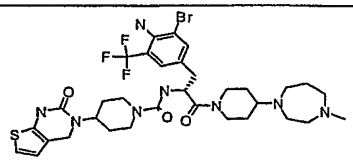
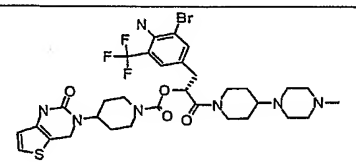
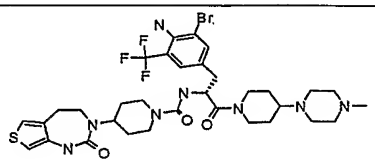
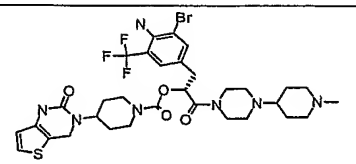
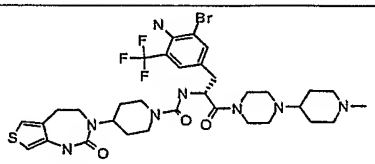
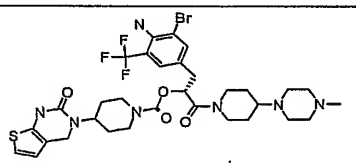
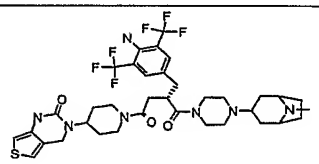
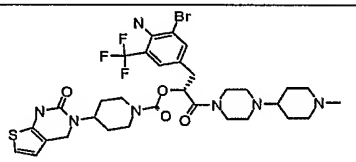
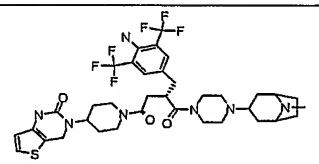
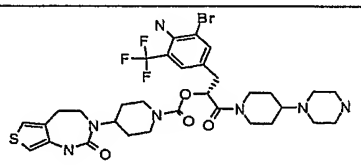
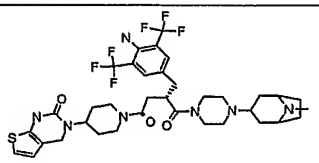
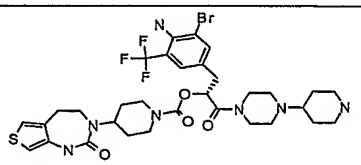
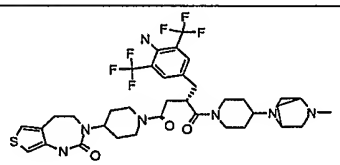
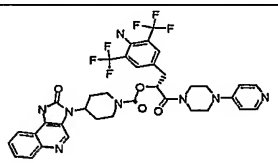
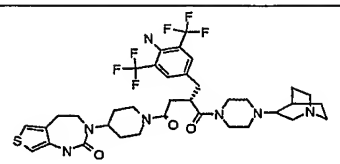
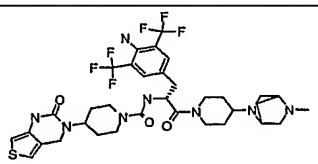
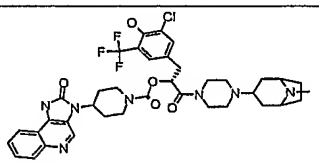
1901		2051	
1902		2052	
1903		2053	
1904		2054	
1905		2055	
1906		2056	
1907		2057	
1908		2058	
1909		2059	
1910		2060	

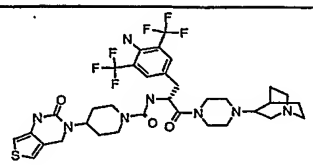
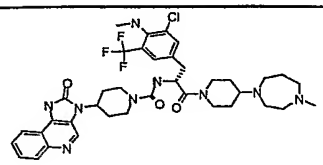
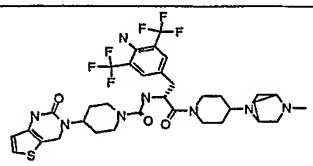
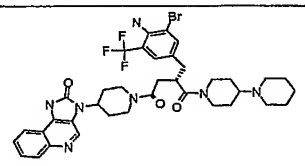
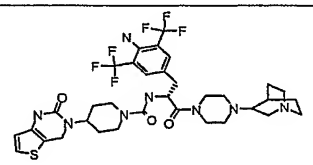
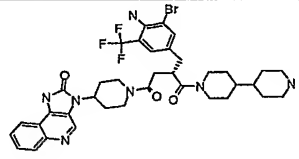
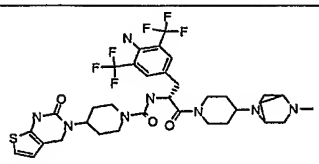
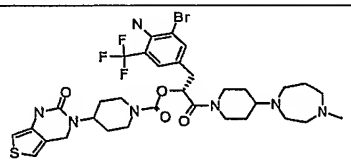
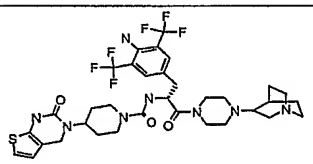
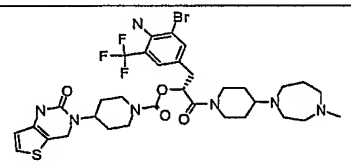
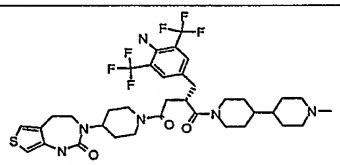
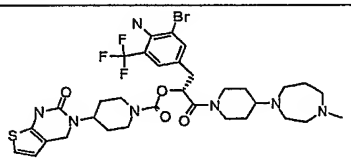
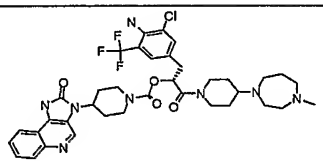
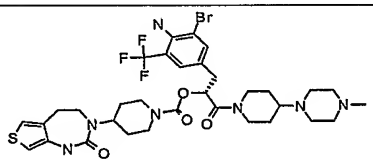
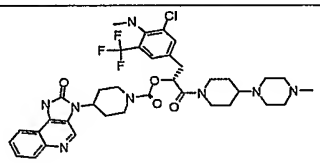
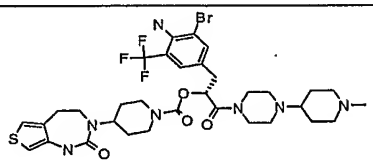
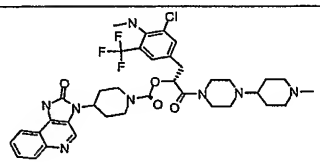
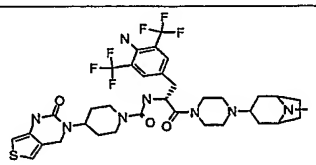
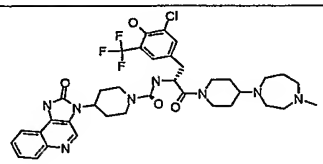
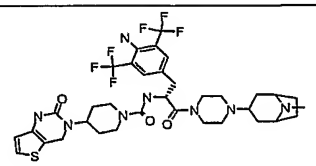
1911		2061	
1912		2062	
1913		2063	
1914		2064	
1915		2065	
1916		2066	
1917		2067	
1918		2068	
1919		2069	
1920		2070	

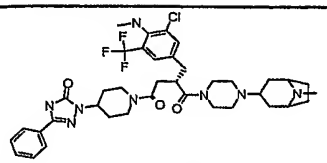
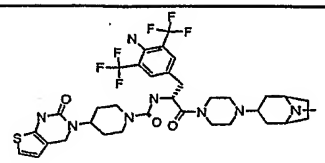
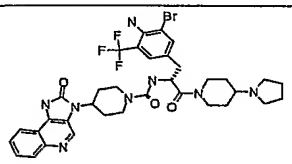
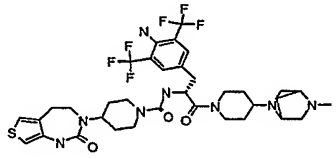
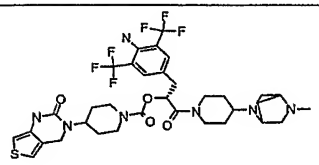
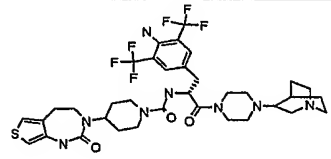
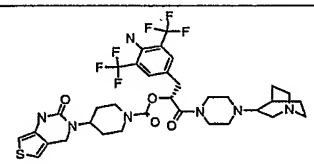
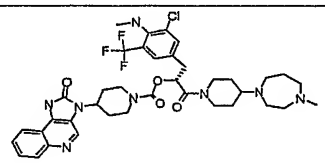
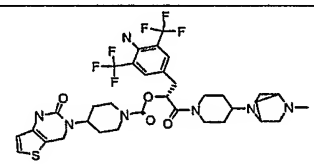
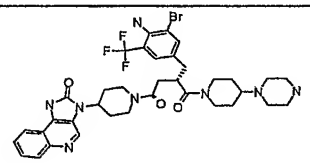
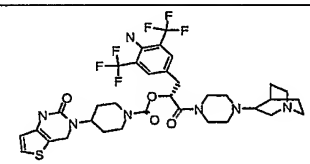
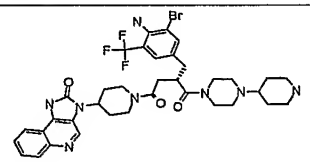
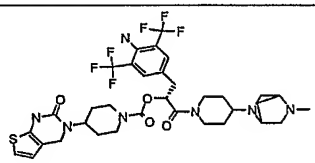
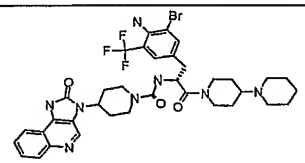
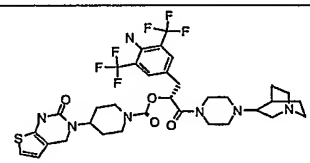
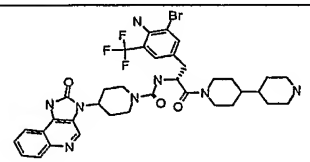
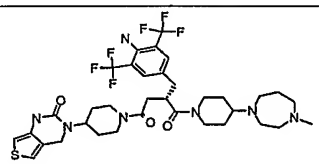
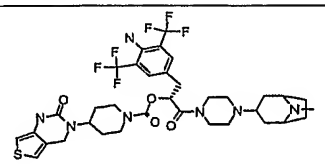
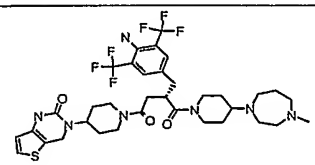
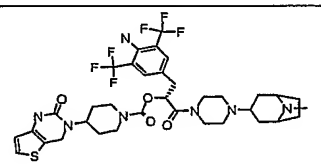
1921		2071	
1922		2072	
1923		2073	
1924		2074	
1925		2075	
1926		2076	
1927		2077	
1928		2078	
1929		2079	
1930		2080	

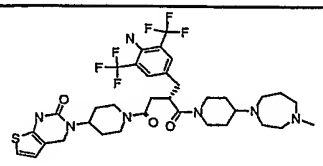
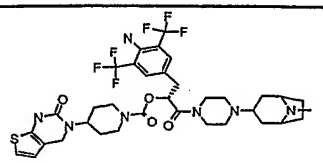
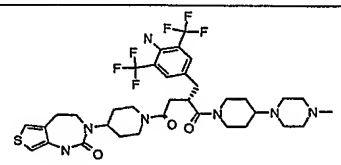
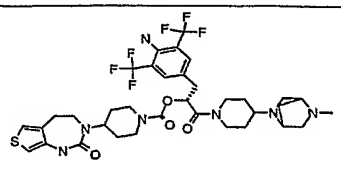
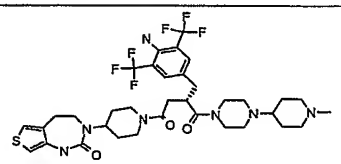
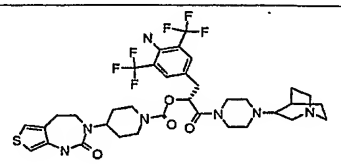
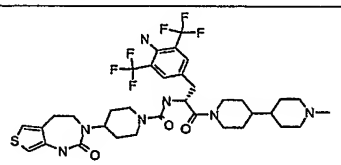
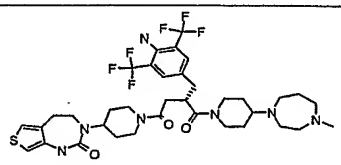
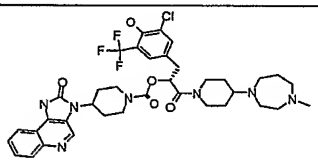
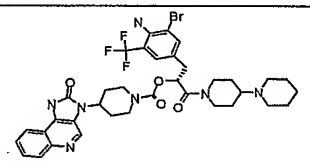
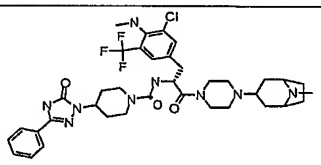
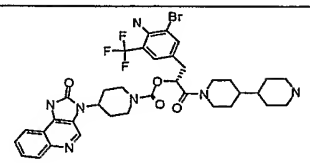
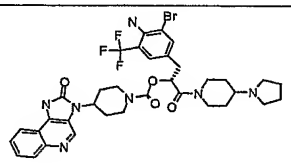
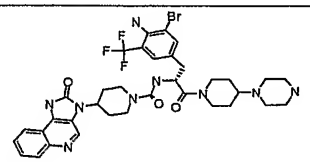
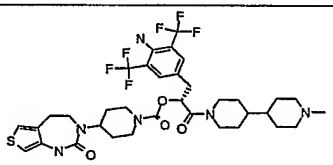
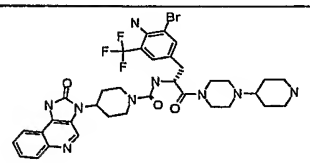
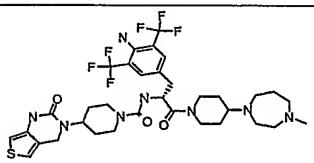
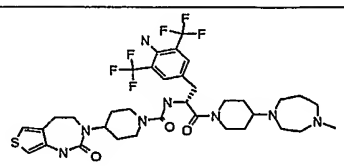
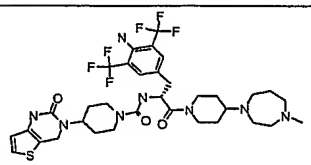
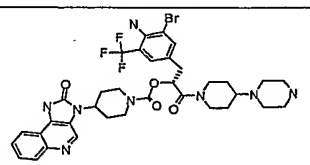
1931		2081	
1932		2082	
1933		2083	
1934		2084	
1935		2085	
1936		2086	
1937		2087	
1938		2088	
1939		2089	
1940		2090	

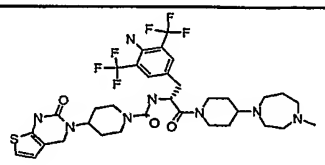
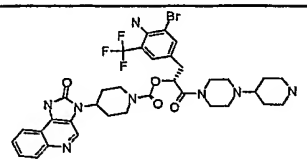
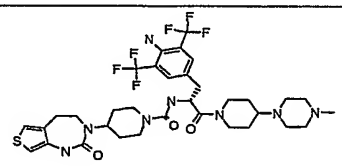
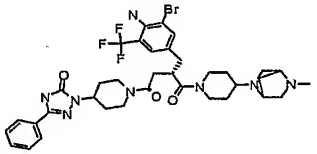
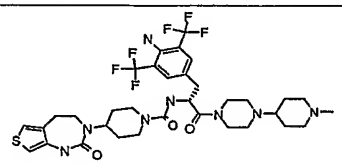
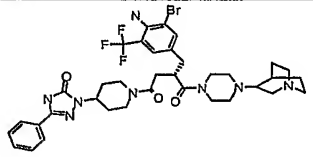
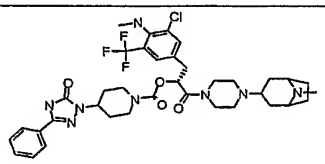
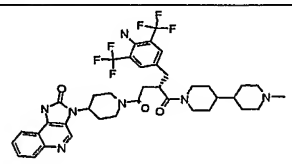
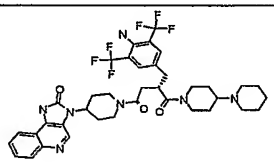
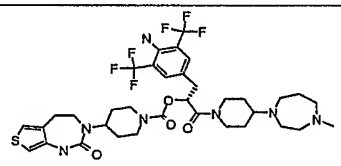
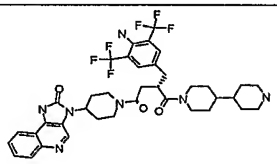
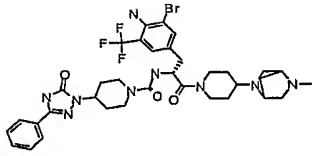
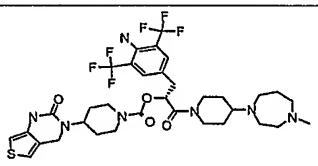
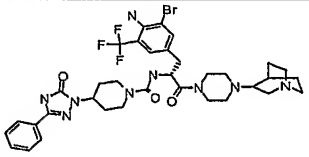
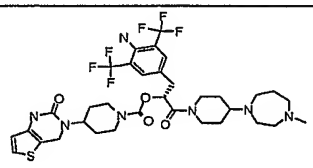
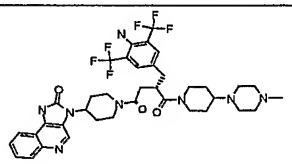
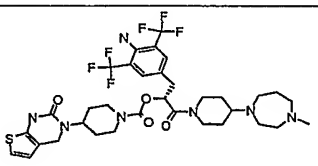
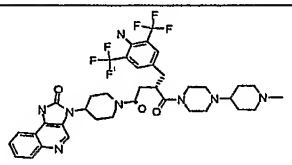
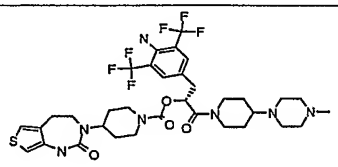
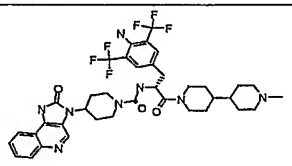
1941		2091	
1942		2092	
1943		2093	
1944		2094	
1945		2095	
1946		2096	
1947		2097	
1948		2098	
1949		2099	
1950		2100	

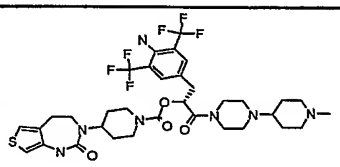
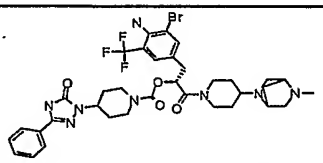
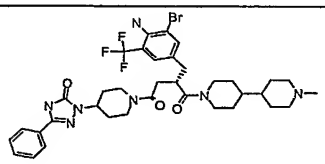
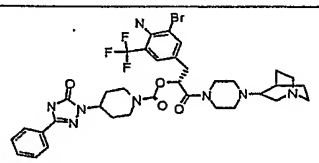
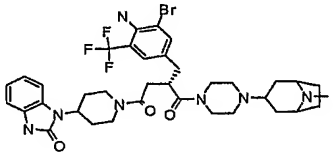
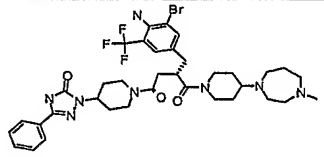
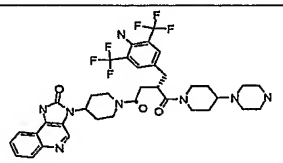
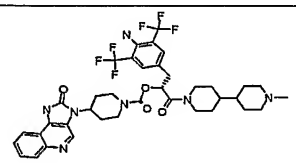
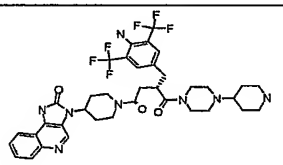
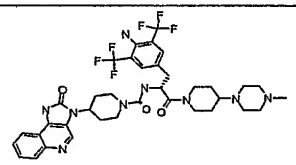
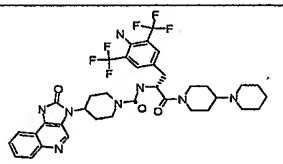
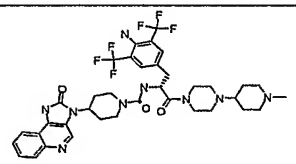
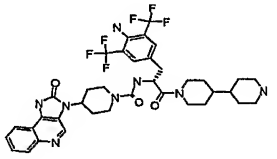
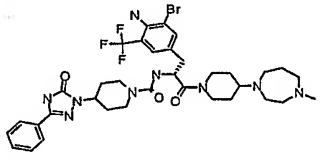
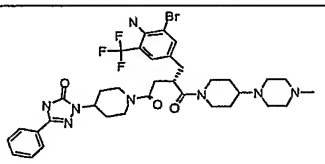
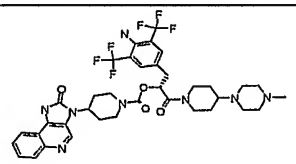
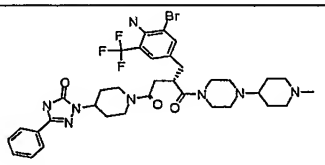
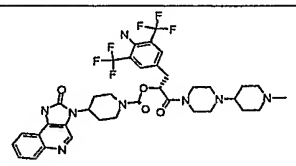
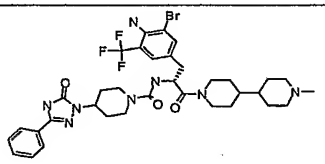
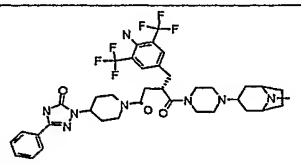
2101		2228	
2102		2229	
2103		2230	
2104		2231	
2105		2232	
2106		2233	
2107		2234	
2108		2235	
2109		2236	
2110		2237	

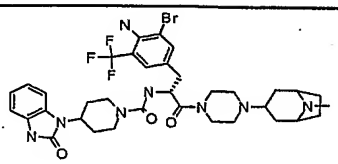
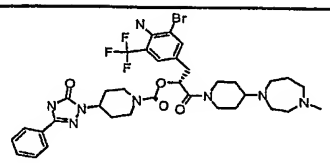
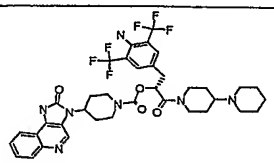
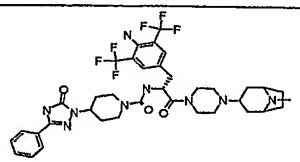
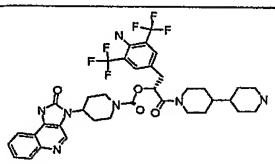
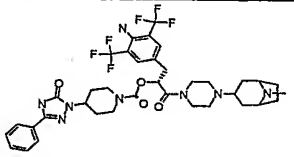
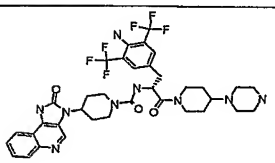
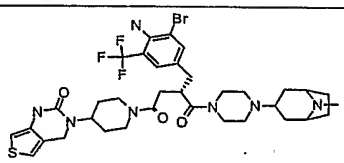
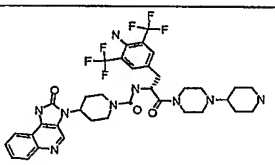
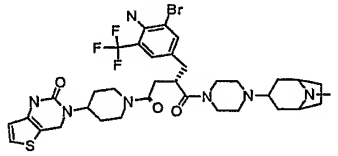
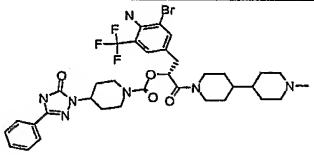
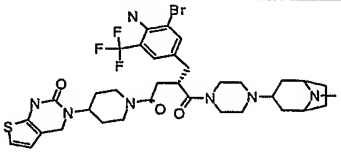
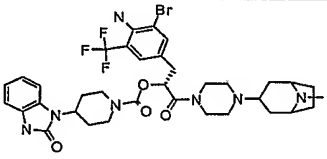
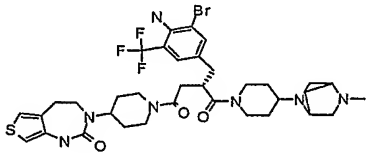
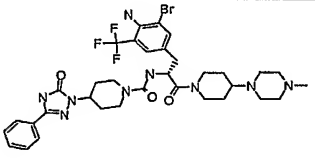
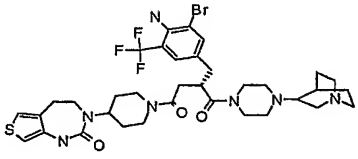
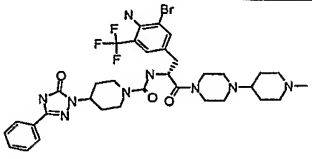
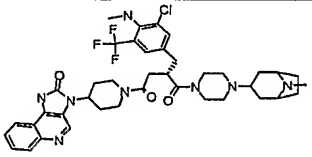
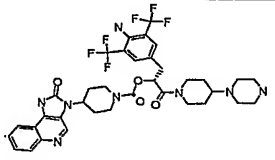
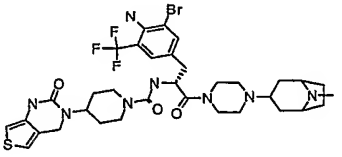
2111		2238	
2112		2239	
2113		2240	
2114		2241	
2115		2242	
2116		2243	
2117		2244	
2118		2245	
2119		2246	
2120		2247	

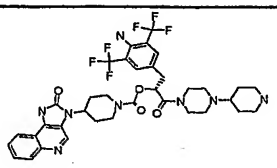
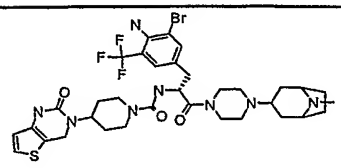
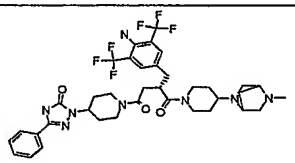
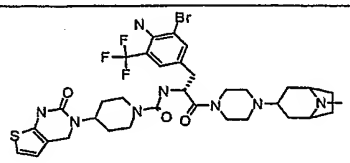
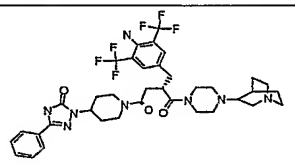
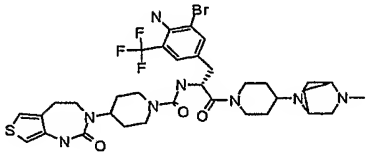
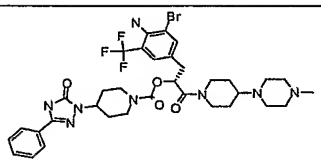
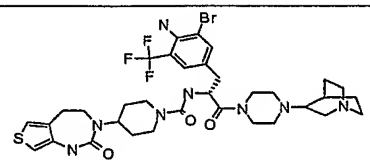
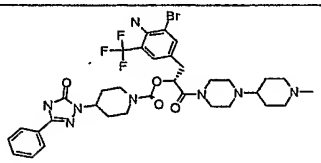
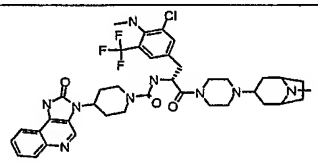
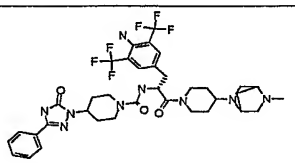
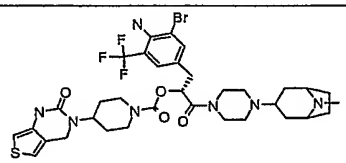
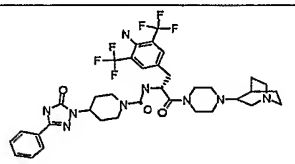
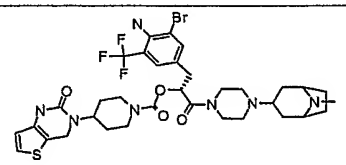
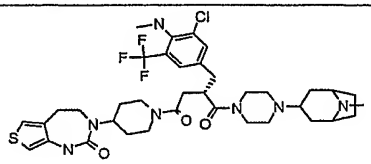
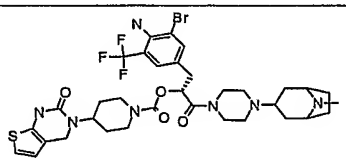
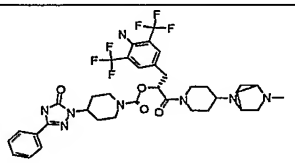
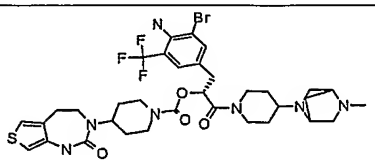
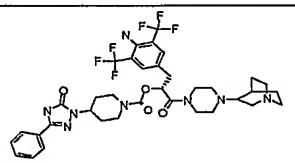
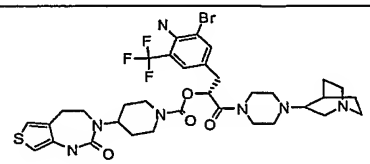
2121		2248	
2122		2249	
2123		2250	
2124		2251	
2125		2252	
2126		2253	
2127		2254	
2128		2255	
2129		2256	
2130		2257	

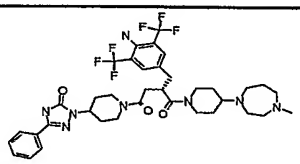
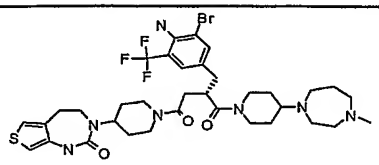
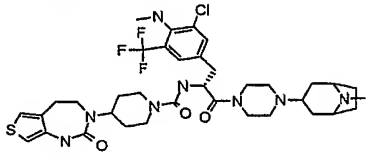
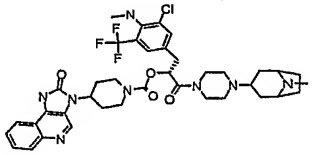
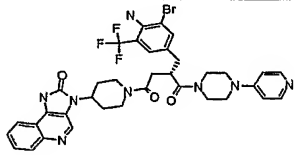
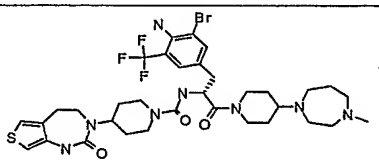
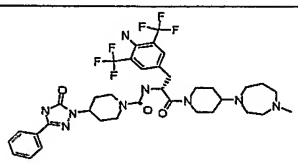
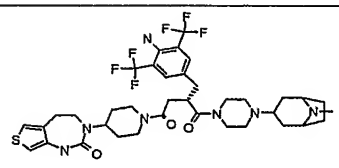
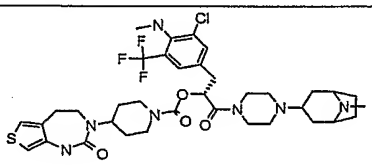
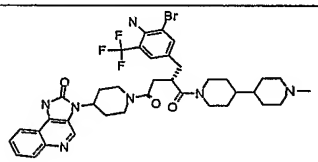
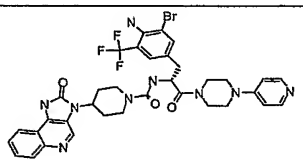
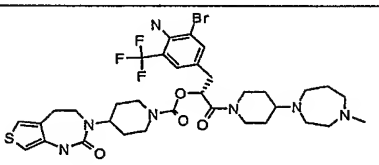
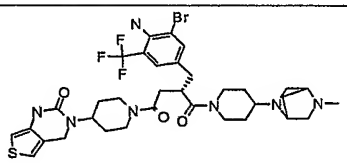
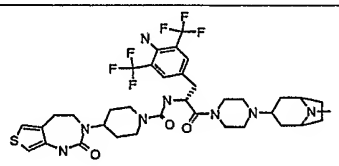
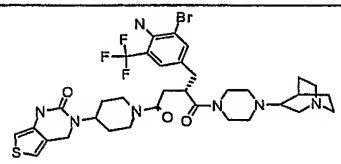
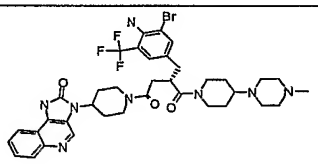
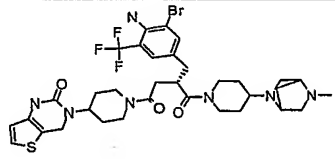
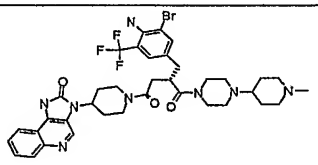
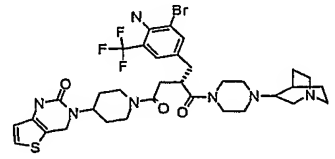
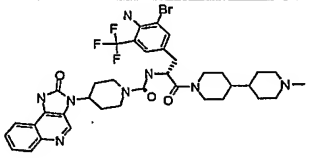
2131		2258	
2132		2259	
2133		2260	
2134		2261	
2135		2262	
2136		2263	
2137		2264	
2138		2265	
2139		2266	
2140		2267	

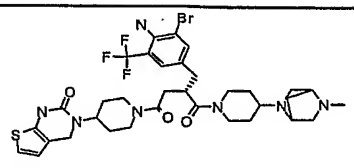
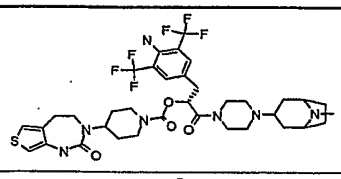
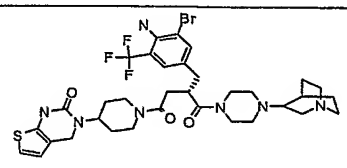
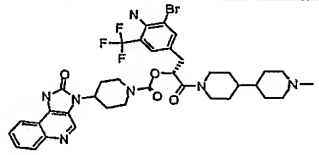
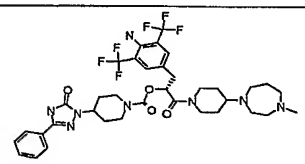
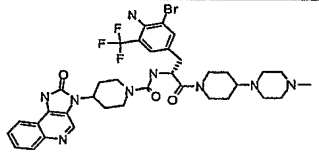
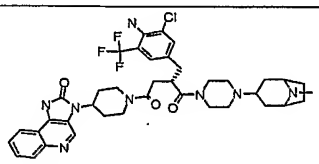
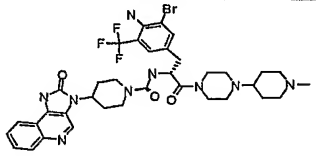
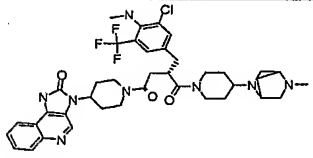
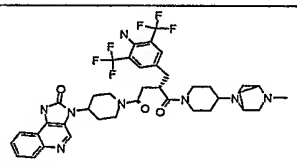
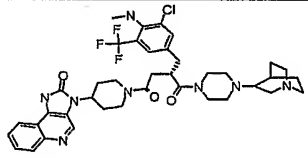
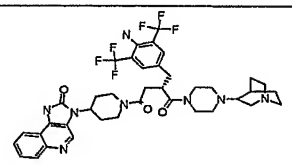
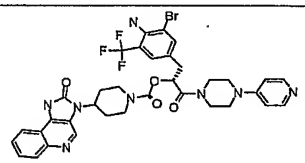
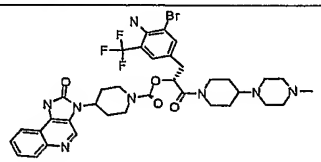
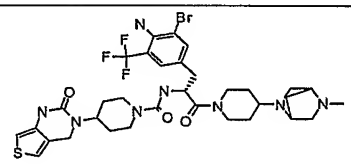
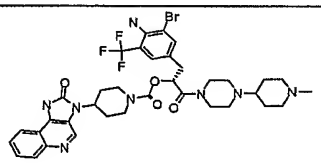
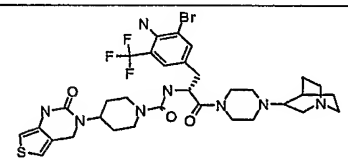
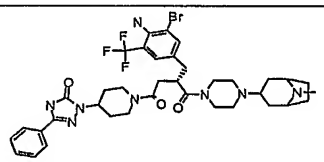
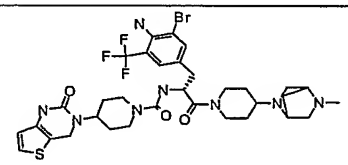
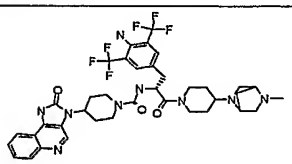
2141		2268	
2142		2269	
2143		2270	
2144		2271	
2145		2272	
2146		2273	
2147		2274	
2148		2275	
2149		2276	
2150		2277	

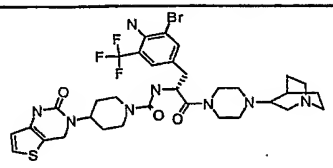
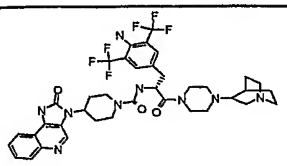
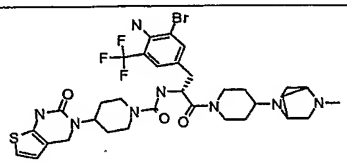
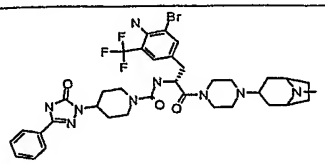
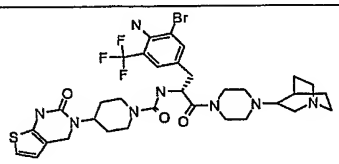
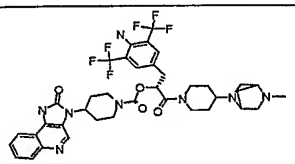
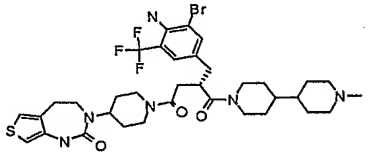
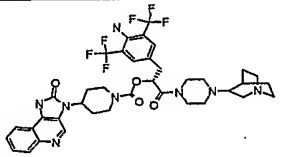
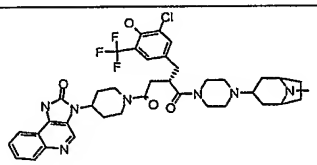
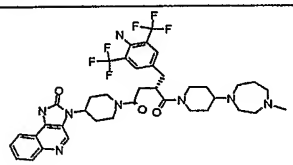
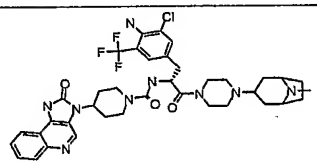
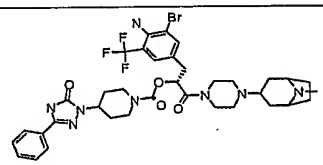
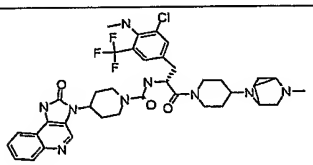
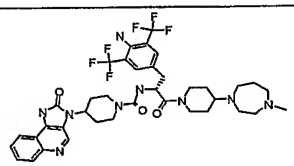
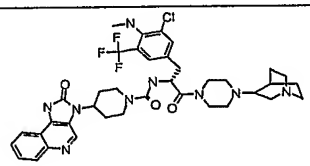
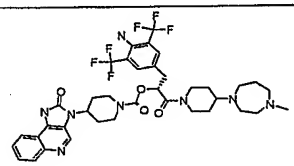
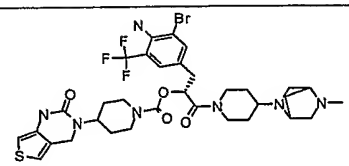
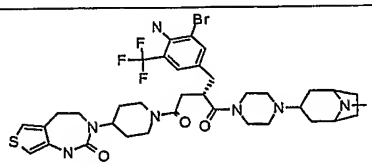
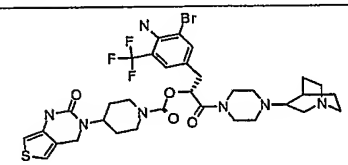
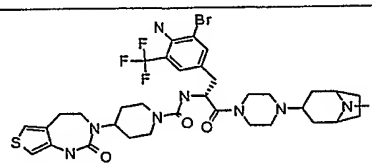
2151		2278	
2152		2279	
2153		2280	
2154		2281	
2155		2282	
2156		2283	
2157		2284	
2158		2285	
2159		2286	
2160		2287	

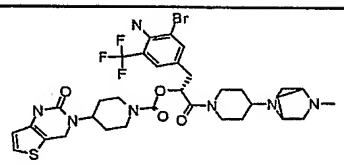
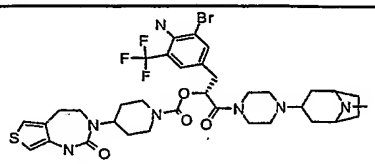
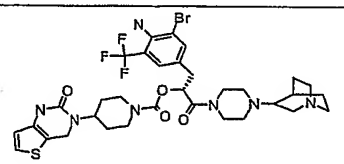
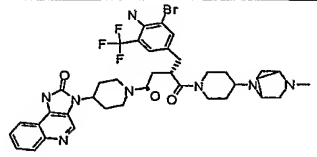
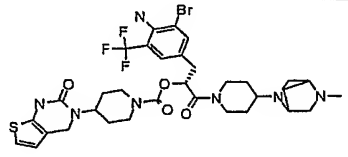
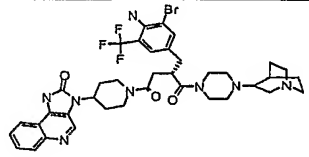
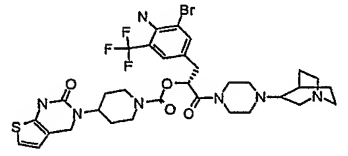
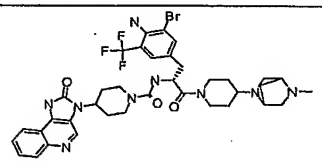
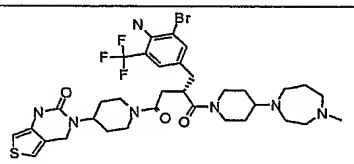
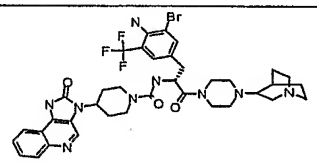
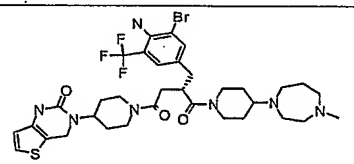
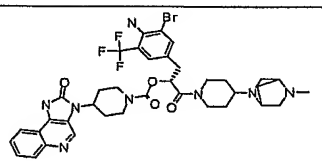
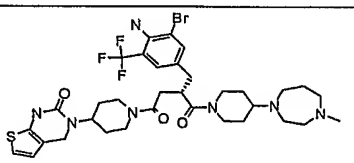
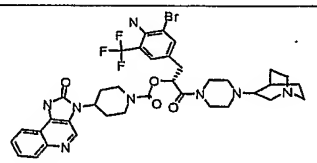
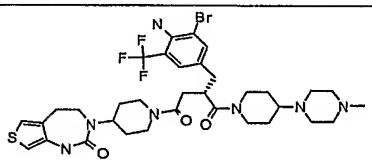
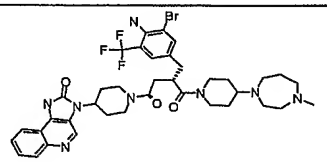
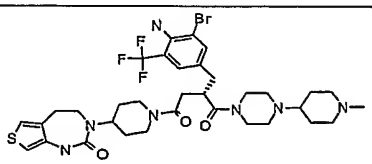
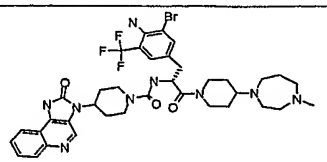
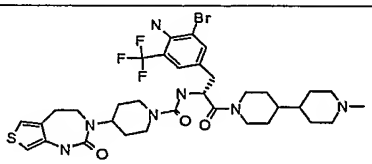
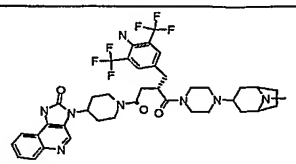
2161		2288	
2162		2289	
2163		2290	
2164		2291	
2165		2292	
2166		2293	
2167		2294	
2168		2295	
2169		2296	
2170		2297	

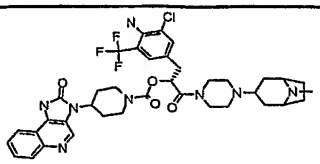
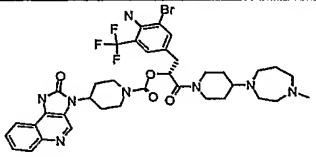
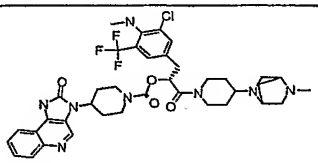
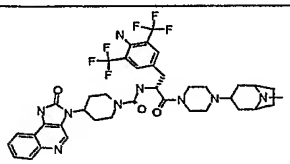
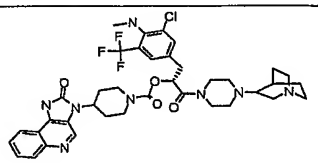
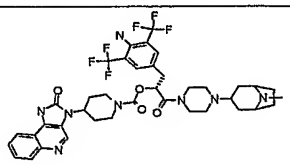
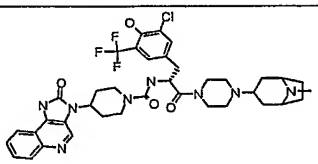
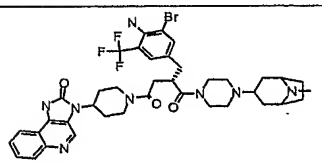
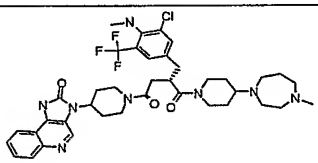
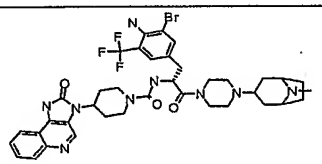
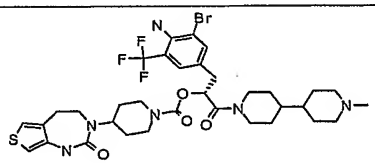
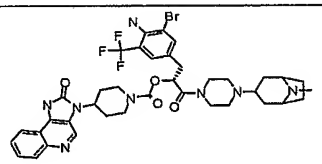
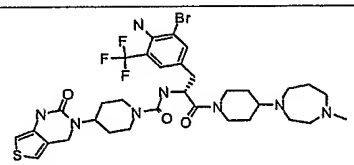
2171		2298	
2172		2299	
2173		2300	
2174		2301	
2175		2302	
2176		2303	
2177		2304	
2178		2305	
2179		2306	
2180		2307	

2181		2308	
2182		2309	
2183		2310	
2184		2311	
2185		2312	
2186		2313	
2187		2314	
2188		2315	
2189		2316	
2190		2317	

2191		2318	
2192		2319	
2193		2320	
2194		2321	
2195		2322	
2196		2323	
2197		2324	
2198		2325	
2199		2326	
2200		2327	

2201		2328	
2202		2329	
2203		2330	
2204		2331	
2205		2332	
2206		2333	
2207		2334	
2208		2335	
2209		2336	
2210		2337	

2211		2338	
2212		2339	
2213		2340	
2214		2341	
2215		2342	
2216		2343	
2217		2344	
2218		2345	
2219		2346	
2220		2347	

2221		2348	
2222		2349	
2223		2350	
2224		2351	
2225		2352	
2226		2353	
2227			

deren Tautomere, deren Diastereomere, deren Enantiomere, deren Hydrate, deren Gemische und deren Salze sowie die Hydrate der Salze, wobei den Verbindungen

(1) 4-(2-Oxo-1,2-dihydro-imidazo[4,5-*c*]chinolin-3-yl)-piperidin-1-carbonsäure-(*R*)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-[1,4']bipiperidinyl-1'-yl-2-oxo-ethylester,

(2) 4-(2-Oxo-1,2-dihydro-imidazo[4,5-*c*]chinolin-3-yl)-piperidin-1-carbonsäure-(*R*)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-2-oxo-ethylester,

(3) 4-(2-Oxo-1,2-dihydro-imidazo[4,5-*c*]chinolin-3-yl)-piperidin-1-carbonsäure-(*R*)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-[4-(1-methyl-piperidin-4-yl)-piperazin-1-yl]-2-oxo-ethylester,

(4) 4-(2-Oxo-1,2-dihydro-imidazo[4,5-*c*]chinolin-3-yl)-piperidin-1-carbonsäure-(*R*)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-(1'-methyl-[4,4']bipiperidinyl-1-yl)-2-oxo-ethylester,

(5) 4-(5-Oxo-3-phenyl-4,5-dihydro-[1,2,4]triazol-1-yl)-piperidin-1-carbonsäure-(*R*)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-2-oxo-ethylester,

(6) 4-(5-Oxo-3-phenyl-4,5-dihydro-[1,2,4]triazol-1-yl)-piperidin-1-carbonsäure (R)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-[4-(1-methyl-piperidin-4-yl)-piperazin-1-yl]-2-oxo-ethylester,

(7) 4-(5-Oxo-3-phenyl-4,5-dihydro-[1,2,4]triazol-1-yl)-piperidin-1-carbonsäure-(R)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-(1'-methyl-[4,4']bipiperidinyl-1-yl)-2-oxo-ethylester,

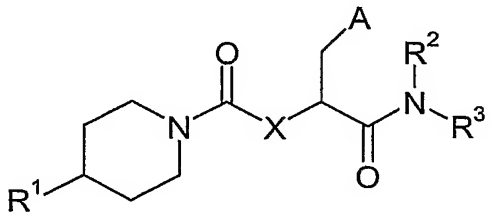
(8) 4-(5-Oxo-3-phenyl-4,5-dihydro-[1,2,4]triazol-1-yl)-piperidin-1-carbonsäure-(*R*)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-[1,4']bipiperidinyl-1'-yl-2-oxo-ethylester,

(9) 4-(5-Oxo-3-phenyl-4,5-dihydro-[1,2,4]triazol-1-yl)-piperidin-1-carbonsäure-(*R*)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-[4-(1-aza-bicyclo[2.2.2]oct-3-yl)-piperazin-1-yl]-2-oxo-ethylester,

deren Tautomeren, deren Diastereomeren, deren Enantiomeren, deren Hydraten, deren Gemischen und deren Salzen sowie den Hydraten der Salze eine herausragende Bedeutung zukommt.

Die Verbindungen der allgemeinen Formel (I) werden nach prinzipiell bekannten Methoden hergestellt. Die folgenden Verfahren haben sich zur Herstellung der erfindungsgemäßen Verbindungen der allgemeinen Formel (I) besonders bewährt:

(a) Zur Herstellung von Verbindungen der allgemeinen Formel



, (I)

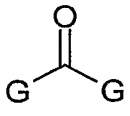
in der X das Sauerstoffatom oder die NH-Gruppe bedeutet und A und R^1 bis R^3 wie eingangs erwähnt definiert sind:

Umsetzung eines Piperidins der allgemeinen Formel

, (III)

in der R^1 wie eingangs erwähnt definiert ist,

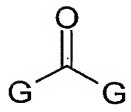
(i) mit einem Kohlensäurederivat der allgemeinen Formel



, (IV)

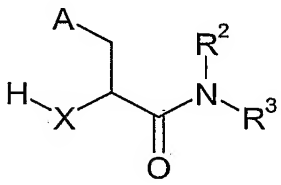
in der G eine nucleofuge Gruppe, die gleich oder verschieden sein kann, bevorzugt die Phenoxy-, 1*H*-Imidazol-1-yl-, 1*H*-1,2,4-Triazol-1-yl-, Trichlormethoxy- oder die 2,5-Dioxopyrrolidin-1-yloxy-Gruppe, bedeutet, mit der Maßgabe, dass X die NH-Gruppe darstellt, oder

(ii) mit einem Kohlensäurederivat der allgemeinen Formel


, (IV)

in der G eine nucleofuge Gruppe, die gleich oder verschieden sein kann, bevorzugt das Chloratom, die *p*-Nitrophenoxy- oder Trichlormethoxy-Gruppe, bedeutet, mit der Maßgabe, dass X das Sauerstoffatom bedeutet,

und mit einer Verbindung der allgemeinen Formel

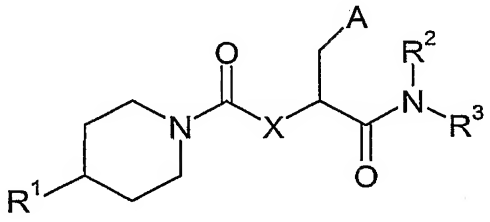

, (V)

in der X das Sauerstoffatom oder eine NH-Gruppe bedeutet und A, R^2 und R^3 wie eingangs erwähnt definiert sind, mit der Maßgabe, dass R^2 und R^3 keine weitere freie primäre oder sekundäre aliphatische Aminofunktion enthalten.
Eine gegebenenfalls in dem Rest $-NR^2R^3$ zusätzlich vorhandene primäre oder sekundäre Aminofunktion wird jeweils mit einer geeigneten Schutzgruppe versehen.

Die im Prinzip zweistufigen Reaktionen werden in der Regel als Eintopfverfahren durchgeführt, und zwar bevorzugt in der Weise, dass man in der ersten Stufe eine der beiden Komponenten (III) oder (V) mit äquimolaren Mengen des Kohlensäurederivates der allgemeinen Formel (IV) in einem geeigneten Lösemittel bei tieferer Temperatur zur Reaktion bringt, anschließend wenigstens äquimolare Mengen der anderen Komponente (III) oder (V) zugibt und die Umsetzung bei höherer Temperatur beendet. Die Umsetzungen mit Bis-(trichlormethyl)-carbonat werden bevorzugt in Gegenwart von wenigstens 2 Äquivalenten (bezogen auf Bis-(trichlormethyl)-carbonat) einer tertiären Base, beispielsweise von Triethylamin, *N*-Ethyldiisopropylamin, Pyridin, 1,5-Diaza-bicyclo-[4.3.0]-non-5-en, 1,4-Diazabicyclo-[2.2.2]octan oder 1,8-Diazabicyclo-[5.4.0]-un-dec-7-en, durchgeführt. Als Lösungsmittel, die wasserfrei sein sollten, kommen beispielsweise Tetrahydrofuran, Dioxan,

Dimethylformamid, Dimethylacetamid, *N*-Methyl-2-pyrrolidon, 1,3-Dimethyl-2-imidazolidinon oder Acetonitril in Betracht, bei Verwendung von Bis-(trichlormethyl)-carbonat als Carbonylkomponente werden wasserfreie Chlorkohlenwasserstoffe, beispielsweise Dichlormethan, 1,2-Dichlorethan oder Trichlorethylen, bevorzugt. Die Reaktionstemperaturen liegen für die erste Reaktionsstufe zwischen –30°C und +25°C, bevorzugt –5°C und +10°C, für die zweite Reaktionsstufe zwischen +15°C und der Siedetemperatur des verwendeten Lösemittels, bevorzugt zwischen +20°C und +70°C (Siehe auch: H. A. Staab und W. Rohr, "Synthesen mit heterocyclischen Amiden (Azoliden)", Neuere Methoden der Präparativen Organischen Chemie, Band V, S. 53-93, Verlag Chemie, Weinheim/Bergstr., 1967; P. Majer und R.S. Randad, J. Org. Chem. 59, S. 1937-1938 (1994); K. Takeda, Y. Akagi, A. Saiki, T. Sukahara und H. Ogura, Tetrahedron Letters 24 (42), 4569-4572 (1983); S.R. Sandler und W. Karo in "Organic Functional Group Preparations", Vol. II, S. 223-245, Academis Press, New York 1971).

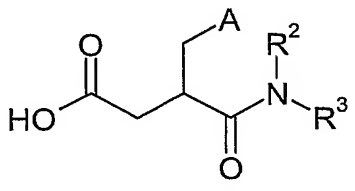
(b) Zur Herstellung von Verbindungen der allgemeinen Formel



, (I)

in der X die Methylengruppe bedeutet und A und R^1 bis R^3 wie eingangs erwähnt definiert sind, mit der Maßgabe, dass keine weitere freie primäre oder sekundäre aliphatische Aminofunktion im Molekül enthalten ist:

Kupplung einer Carbonsäure der allgemeinen Formel



, (VI)

in der A, R^2 und R^3 wie eingangs erwähnt definiert sind, mit einem Piperidin der allgemeinen Formel

, (III)

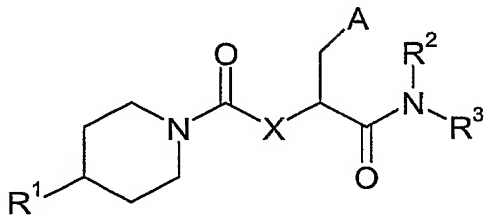
in der R^1 die eingangs erwähnten Bedeutungen besitzt.

Die Kupplung wird bevorzugt unter Verwendung von aus der Peptidchemie bekannten Verfahren (siehe z. B. Houben-Weyl, Methoden der Organischen Chemie, Bd. 15/2) durchgeführt, wobei zum Beispiel Carbodiimide, wie z.B. Dicyclohexylcarbodiimid (DCC), Diisopropylcarbodiimid (DIC) oder Ethyl-(3-dimethylaminopropyl)-carbodiimid, O-(1*H*-Benzotriazol-1-yl)-*N*,*N*-*N*',*N*'-tetramethyluronium-hexafluorphosphat (HBTU) oder -tetrafluorborat (TBTU) oder 1*H*-Benzotriazol-1-yl-oxy-tris-(dimethylamino)-phosphoniumhexafluorphosphat (BOP) eingesetzt werden. Durch Zugabe von 1-Hydroxybenzotriazol (HOBt) oder von 3-Hydroxy-4-oxo-3,4-dihydro-1,2,3-benzotriazin (HOOBt) kann die Reaktionsgeschwindigkeit gesteigert werden. Die Kupplungen werden normalerweise mit äquimolaren Anteilen der Kupplungskomponenten sowie des Kupplungsreagenz in Lösemitteln wie Dichlormethan, Tetrahydrofuran, Acetonitril, Dimethylformamid (DMF), Dimethylacetamid (DMA), *N*-Methylpyrrolidon (NMP) oder Gemischen aus diesen und bei Temperaturen zwischen –30°C und +30°C, bevorzugt –20°C und +25°C, durchgeführt. Sofern erforderlich, wird als zusätzliche Hilfsbase *N*-Ethyldiisopropylamin (DIEA) (Hünig-Base) bevorzugt.

Als weiteres Kupplungsverfahren zur Synthese von Verbindungen der allgemeinen Formel (I) wird das sogenannte "Anhydridverfahren" (siehe auch: M. Bodanszky, "Peptide Chemistry", Springer-Verlag 1988, S. 58-59; M. Bodanszky, "Principles of Peptide Synthesis", Springer-Verlag 1984, S. 21-27) eingesetzt. Bevorzugt wird das "gemischte Anhydridverfahren" in der Variante nach Vaughan (J.R. Vaughan Jr., J. Amer. Chem.Soc. 73, 3547 (1951)), bei der unter Verwendung von Chlorkohlensäureisobutylester in Gegenwart von Basen, wie 4-Methylmorpholin oder 4-Ethylmorpholin, das gemischte Anhydrid aus der zu kuppelnden Carbonsäure der

allgemeinen Formel (VI) und dem Kohlensäure-monoisobutylester erhalten wird. Die Herstellung dieses gemischten Anhydrids und die Kupplung mit Aminen erfolgt im Eintopfverfahren, unter Verwendung der vorstehend genannten Lösemittel und bei Temperaturen zwischen -20 und +25°C, bevorzugt 0°C und +25°C.

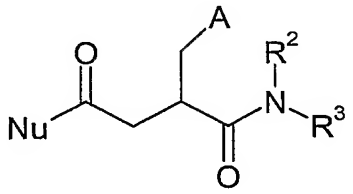
(c) Zur Herstellung von Verbindungen der allgemeinen Formel



, (I)

in der X die Methylengruppe bedeutet und A und R^2 und R^3 wie eingangs erwähnt definiert sind, mit der Maßgabe, dass diese Gruppen kein freies primäres oder sekundäres Amin enthalten:

Kupplung einer Verbindung der allgemeinen Formel



, (VII)

in der A, R^2 und R^3 wie eingangs erwähnt definiert sind, mit der Maßgabe, dass R^2 und R^3 kein freies primäres oder sekundäres Amin enthalten, und Nu eine Austrittsgruppe, beispielsweise ein Halogenatom, wie das Chlor-, Brom- oder Iodatom, eine Alkylsulfonyloxygruppe mit 1 bis 10 Kohlenstoffatomen im Alkylteil, eine gegebenenfalls durch Chlor- oder Bromatome, durch Methyl- oder Nitrogruppen mono-, di- oder trisubstituierte Phenylsulfonyloxy- oder Naphthylsulfonyloxygruppe, wobei die Substituenten gleich oder verschieden sein können, eine 1*H*-Imidazol-1-yl-, eine gegebenenfalls durch eine oder zwei Methylgruppen im Kohlenstoffgerüst substituierte 1*H*-Pyrazol-1-yl-, eine 1*H*-1,2,4-Triazol-1-yl-, 1*H*-1,2,3-Triazol-1-yl-, 1*H*-

1,2,3,4-Tetrazol-1-yl-, eine Vinyl-, Propargyl-, *p*-Nitrophenyl-, 2,4-Dinitrophenyl-, Trichlorphenyl-, Pentachlorphenyl-, Pentafluorphenyl-, Pyranyl- oder Pyridinyl-, eine Dimethylaminyloxy-, 2(1*H*)-Oxopyridin-1-yl-oxy-, 2,5-Dioxopyrrolidin-1-yloxy-, Phthalimidyloxy-, 1*H*-Benzo-triazol-1-yloxy- oder Azidgruppe bedeutet,

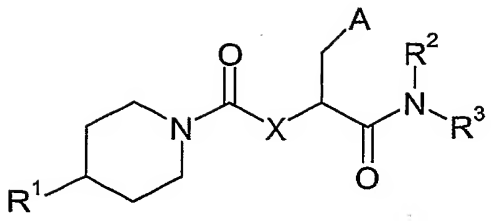
mit einem Piperidin der allgemeinen Formel

, (III)

in der R^1 wie eingangs erwähnt definiert ist.

Die Umsetzung wird unter Schotten-Baumann- oder Einhorn-Bedingungen durchgeführt, das heißt die Komponenten werden in Gegenwart von wenigstens einem Äquivalent einer Hilfsbase bei Temperaturen zwischen -50°C und +120°C, bevorzugt -10°C und +30°C, und gegebenenfalls in Gegenwart von Lösemitteln zur Reaktion gebracht. Als Hilfsbasen kommen bevorzugt Alkali- und Erdalkalihydroxide, beispielsweise Natriumhydroxid, Kaliumhydroxid oder Bariumhydroxid, Alkalicarbonate, z. B. Natriumcarbonat, Kaliumcarbonat oder Cäsiumcarbonat, Alkaliacetate, z.B. Natrium- oder Kaliumacetat, sowie tertiäre Amine, beispielsweise Pyridin, 2,4,6-Tri-methylpyridin, Chinolin, Triethylamin, *N*-Ethyl-diisopropylamin, *N*-Ethyl-dicyclohexyl-amin, 1,4-Di-azabicyclo[2.2.2]octan oder 1,8-Diazabicyclo-[5.4.0]-undec-7-en, als Lösemittel beispielsweise Dichlormethan, Tetrahydrofuran, 1,4-Dioxan, Acetonitril, Dimethylformamid, Dimethylacetamid, *N*-Methylpyrrolidon oder Gemische davon in Betracht; werden als Hilfsbasen Alkali- oder Erdalkalihydroxide, Alkalicarbonate oder -acetate verwendet, kann dem Reaktionsgemisch auch Wasser als Cosolvens zugesetzt werden.

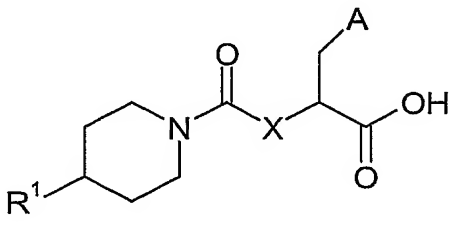
(d) Zur Herstellung von Verbindungen der allgemeinen Formel



, (I)

in der A, X und R^1 bis R^3 wie eingangs erwähnt definiert sind:

Kupplung einer Carbonsäure der allgemeinen Formel



, (VIII)

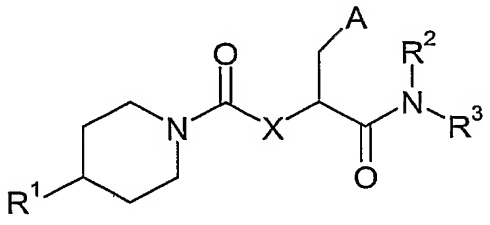
in der A, X und R^1 wie eingangs erwähnt definiert sind, mit einem Amin der allgemeinen Formel HNR^2R^3, in der R^2 und R^3 wie eingangs definiert sind, mit der Maßgabe, dass sie keine weitere freie primäre oder sekundäre aliphatische Aminofunktion enthalten.

Die Kupplung wird bevorzugt unter Verwendung von aus der Peptidchemie bekannten Verfahren (siehe z. B. Houben-Weyl, Methoden der Organischen Chemie, Band 15/2) durchgeführt, wobei zum Beispiel Carbodiimide, wie z.B. Dicyclohexylcarbodiimid (DCC), Diisopropylcarbodiimid (DIC) oder Ethyl-(3-dimethylamino-propyl)-carbodiimid, *O*-(1*H*-Benzotriazol-1-yl)-*N*,*N*-*N*',*N*'-tetramethyluronium-hexafluorphosphat (HBTU) oder -tetrafluorborat (TBTU) oder 1*H*-Benzotriazol-1-yl-oxy-tris-(dimethylamino)-phosphoniumhexafluorphosphat (BOP) eingesetzt werden. Durch Zugabe von 1-Hydroxybenzotriazol (HOBt) oder von 3-Hydroxy-4-oxo-3,4-dihydro-1,2,3-benzotriazin (HOOBt) kann die Reaktionsgeschwindigkeit gesteigert werden. Die Kupplungen werden normalerweise mit äquimolaren Anteilen der Kupplungskomponenten sowie des Kupplungsreagenz in Lösungsmitteln wie Dichlormethan, Tetrahydrofuran, Acetonitril, Dimethylformamid (DMF), Dimethylacetamid (DMA), *N*-Methylpyrrolidon (NMP) oder Gemischen aus diesen und bei Temperaturen

zwischen -30 und +30°C, bevorzugt -20 und +25°C, durchgeführt. Sofern erforderlich wird als zusätzliche Hilfsbase *N*-Ethyldiisopropylamin (DIEA) (Hünig-Base) bevorzugt.

Als weiteres Kupplungsverfahren zur Synthese von Verbindungen der allgemeinen Formel (I) wird das sogenannte "Anhydridverfahren" (siehe auch: M. Bodanszky, "Peptide Chemistry", Springer-Verlag 1988, S. 58-59; M. Bodanszky, "Principles of Peptide Synthesis", Springer-Verlag 1984, S. 21-27) eingesetzt. Bevorzugt wird das "gemischte Anhydridverfahren" in der Variante nach Vaughan (J.R. Vaughan Jr., J. Amer. Chem.Soc. 73, 3547 (1951)), bei der unter Verwendung von Chlorkohlensäureisobutylester in Gegenwart von Basen, wie 4-Methylmorpholin oder 4-Ethylmorpholin, das gemischte Anhydrid aus der zu kuppelnden Carbonsäure der allgemeinen Formel (VIII) und dem Kohlensäuremonoisobutylester erhalten wird. Die Herstellung dieses gemischten Anhydrids und die Kupplung mit den Aminen der allgemeinen Formel HNR^2R^3 erfolgt im Eintopfverfahren, unter Verwendung der vorstehend genannten Lösemittel und bei Temperaturen zwischen –20°C und +25°C, bevorzugt zwischen 0°C und +25°C.

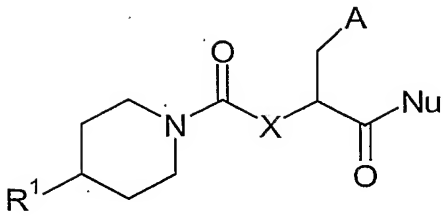
(e) Zur Herstellung von Verbindungen der allgemeinen Formel



, (I)

in der A, X und R^1 bis R^3 wie eingangs erwähnt definiert sind, mit der Maßgabe, dass kein freies primäres oder sekundäres Amin im Molekül enthalten ist:

Kupplung einer Verbindung der allgemeinen Formel



, (IX)

in der A, X und R^1 wie eingangs erwähnt definiert sind und Nu eine Austrittsgruppe, beispielsweise ein Halogenatom, wie das Chlor-, Brom- oder Iodatom, eine Alkylsulfonyloxygruppe mit 1 bis 10 Kohlenstoffatomen im Alkylteil, eine gegebenenfalls durch Chlor- oder Bromatome, durch Methyl- oder Nitrogruppen mono-, di- oder trisubstituierte Phenylsulfonyloxy- oder Naphthylsulfonyloxygruppe, wobei die Substituenten gleich oder verschieden sein können, eine 1*H*-Imidazol-1-yl-, eine gegebenenfalls durch eine oder zwei Methylgruppen im Kohlenstoffgerüst substituierte 1*H*-Pyrazol-1-yl-, eine 1*H*-1,2,4-Triazol-1-yl-, 1*H*-1,2,3-Triazol-1-yl-, 1*H*-1,2,3,4-Tetrazol-1-yl-, eine Vinyl-, Propargyl-, *p*-Nitrophenyl-, 2,4-Dinitrophenyl-, Trichlorphenyl-, Pentachlorphenyl-, Pentafluorphenyl-, Pyranyl- oder Pyridinyl-, eine Dimethylaminyloxy-, 2(1*H*)-Oxopyridin-1-yl-oxy-, 2,5-Dioxopyrrolidin-1-yloxy-, Phthalimidyloxy-, 1*H*-Benzo-triazol-1-yloxy- oder Azidgruppe bedeutet,

mit einem Amin der allgemeinen Formel HNR^2R^3, in der R^2 und R^3 wie eingangs definiert sind, mit der Maßgabe, dass keine freie Carbonsäure- und/oder keine weitere freie primäre oder sekundäre aliphatische Aminofunktion enthalten ist.

Die Umsetzung wird unter Schotten-Baumann- oder Einhorn-Bedingungen durchgeführt, das heißt, die Komponenten werden in Gegenwart von wenigstens einem Äquivalent einer Hilfsbase bei Temperaturen zwischen -50°C und +120°C, bevorzugt -10°C und +30°C, und gegebenenfalls in Gegenwart von Lösungsmitteln zur Reaktion gebracht. Als Hilfsbasen kommen bevorzugt Alkali- und Erdalkalihydroxide, beispielsweise Natriumhydroxid, Kaliumhydroxid oder Bariumhydroxid, Alkalicarbonate, z. B. Natriumcarbonat, Kaliumcarbonat oder Cäsiumcarbonat, Alkaliacetate, z.B. Natrium- oder Kaliumacetat, sowie tertiäre Amine, beispielsweise Pyridin, 2,4,6-Trimethylpyridin, Chinolin, Triethylamin, *N*-Ethyldiisopropylamin, *N*-Ethyldicyclohexylamin, 1,4-Di-azabicyclo[2.2.2]octan oder 1,8-Diaza-bicyclo[5.4.0]-undec-7-en, als Lösungsmittel beispielsweise Dichlormethan, Tetrahydrofuran,

1,4-Dioxan, Acetonitril, Dimethylformamid, Dimethylacetamid, *N*-Methylpyrrolidon oder Gemische davon in Betracht; werden als Hilfsbasen Alkali- oder Erdalkalihydroxide, Alkalicarbonate oder -acetate verwendet, kann dem Reaktionsgemisch auch Wasser als Cosolvens zugesetzt werden.

Die erfindungsgemäßen neuen Verbindungen der allgemeinen Formel (I) enthalten ein oder mehrere Chiralitätszentren. Sind beispielsweise zwei Chiralitätszentren vorhanden, dann können die Verbindungen in Form zweier diastereomerer Antipodenpaare auftreten. Die Erfindung umfaßt die einzelnen Isomeren ebenso wie ihre Gemische.

Die Trennung der jeweiligen Diastereomeren gelingt auf Grund ihrer unterschiedlichen physikochemischen Eigenschaften, z.B. durch fraktionierte Kristallisation aus geeigneten Lösemitteln, durch Hochdruckflüssigkeits- oder Säulenchromatographie unter Verwendung chiraler oder bevorzugt achiraler stationärer Phasen.

Die Trennung von unter die allgemeine Formel (I) fallenden Racematen gelingt beispielsweise durch HPLC an geeigneten chiralen stationären Phasen (z. B. Chiral AGP, Chiralpak AD). Racemate, die eine basische Funktion enthalten, lassen sich auch über die diastereomeren, optisch aktiven Salze trennen, die bei Umsetzung mit einer optisch aktiven Säure, beispielsweise (+)- oder (–)-Weinsäure, (+)- oder (–)-Diacetylweinsäure, (+)- oder (–)-Monomethyltartrat oder (+)-Camphersulfonsäure entstehen.

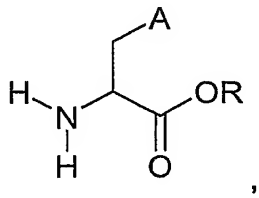
Nach einem üblichen Verfahren zur Isomerentrennung wird das Racemat einer Verbindung der allgemeinen Formel (I) mit einer der vorstehend angegebenen optisch aktiven Säuren in äquimolarer Menge in einem Lösemittel umgesetzt und die erhaltenen kristallinen, diastereomeren, optisch aktiven Salze unter Ausnutzung ihrer verschiedenen Löslichkeit getrennt. Diese Umsetzung kann in jeder Art von Lösemitteln durchgeführt werden, solange sie einen ausreichenden Unterschied hinsichtlich der Löslichkeit der Salze aufweisen. Vorzugsweise werden Methanol, Ethanol oder deren Gemische, beispielsweise im Volumenverhältnis 50:50, verwendet. Sodann wird jedes der optisch aktiven Salze in Wasser gelöst, mit einer

Base, wie Natriumcarbonat oder Kaliumcarbonat, oder mit einer geeigneten Säure, beispielsweise mit verdünnter Salzsäure oder wässeriger Methansulfonsäure, vorsichtig neutralisiert und dadurch die entsprechende freie Verbindung in der (+)- oder (-)-Form erhalten.

Jeweils nur das (*R*)- oder (*S*)-Enantiomer bzw. ein Gemisch zweier optisch aktiver, unter die allgemeine Formel (I) fallender diastereomerer Verbindungen wird auch dadurch erhalten, dass man die oben beschriebenen Synthesen mit jeweils einer geeigneten (*R*)- bzw. (*S*)-konfigurierten Reaktionskomponente durchführt.

Die Ausgangsverbindungen der allgemeinen Formel (III) erhält man, soweit sie nicht literaturbekannt oder gar käuflich sind, entsprechend den in der internationalen Patentanmeldung WO 98/11128 und DE 199 52 146 angegebenen Verfahren. Die Ausgangsverbindungen der allgemeinen Formel (IV) sind käuflich. Verbindungen der allgemeinen Formel (V) lassen sich nach dem Peptidchemiker geläufigen Methoden aus geschützten Phenylalaninen und Aminen der allgemeinen Formel HNR^2R^3 herstellen.

Die zur Herstellung der optisch reinen Verbindungen der allgemeinen Formel (V) nötigen Phenyalaninderivate können aus den Verbindungen der allgemeinen Formel



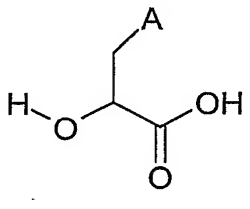
, (X)

in der A wie eingangs erwähnt definiert ist und R eine unverzweigte Alkylgruppe, bevorzugt die Methyl- oder Ethylgruppe, darstellt, durch Racematspaltung hergestellt werden.

Diese Racematspaltung kann mit Hilfe enzymatischer Methoden durchgeführt werden, wobei nur ein Enantiomer des Racemates transformiert wird und das entstehende Gemisch dann mit Hilfe physikochemischer Methoden, bevorzugt mit

Hilfe chromatographischer Methoden, getrennt wird. Ein geeignetes Enzymsystem für diesen Schritt stellt das Enzym Alcalase 2.4 L FG (Novozymes A/S; DK 2880 Bagsvaerd) dar. Die Verbindungen der allgemeinen Formel (X) können dann mit für Peptidchemiker geläufigen Methoden in die enantiomerenreinen Verbindungen der allgemeinen Formel (V) überführt werden.

Falls die Gruppe X in Verbindungen der allgemeinen Formel (V) das Sauerstoffatom darstellt, können die für die Synthese benötigten Hydroxycarbonsäuren der allgemeinen Formel

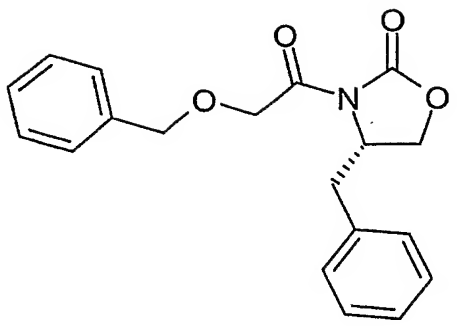


, (XI)

in der A wie eingangs erwähnt definiert ist, aus Verbindungen der allgemeinen Formel (X) gewonnen werden, mit der Maßgabe, dass R das Wasserstoffatom darstellt.

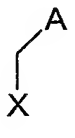
Unter der Maßgabe, dass der Rest A keine Amino- oder Methylaminogruppe enthält, können durch Diazotierung von Verbindungen der allgemeinen Formel (X) mit einem geeigneten Diazotierungsreagenz, bevorzugt Natriumnitrit in saurem Milieu, die Verbindungen der allgemeinen Formel (XI) erhalten werden. Bei Einsatz enantiomerenreiner Verbindungen werden die entsprechenden enantiomerenreinen Hydroxycarbonsäureverbindungen erhalten, wobei die Reaktion unter Retention der Konfiguration abläuft.

Ein weiterer Zugang zu Verbindungen der allgemeinen Formel (XI), in der die Reste A wie eingangs erwähnt definiert sind, besteht in der Alkylierung der Verbindung



, (XII)

mit entsprechend substituierten Benzylchloriden, Benzylbromiden oder Benzyliodiden der allgemeinen Formel

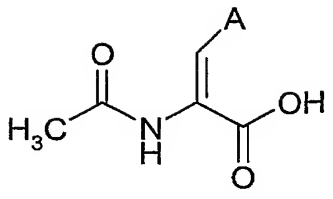


, (XIII)

in der A wie eingangs erwähnt definiert ist und X ein Chlor-, Brom- oder Jodatom bedeutet, in Analogie zu literaturbekannten Methoden (Michael T. Crimmins, Kyle A. Emmitte und Jason D. Katz, Org. Lett. 2, 2165-2167 [2000]).

Die entstehenden diastereomeren Produkte können dann mit Hilfe physikochemischer Methoden, bevorzugt mit Hilfe chromatographischer Methoden, getrennt werden. Die hydrolytische Abspaltung des chiralen Auxiliars, Kupplung mit Aminen der allgemeinen Formel HNR^2R^3 und Abspaltung der Benzylschutzgruppe eröffnet ebenfalls einen Zugang zu enantiomerenreinen Hydroxycarbonsäureverbindungen des allgemeinen Formel (V).

Verbindungen der allgemeinen Formel (XI), in der die Reste A wie eingangs erwähnt definiert sind, können weiterhin durch Verkochen von 2-Acetylamino-3-phenyl-acrylsäuren der allgemeinen Formel



, (XIV)

mittels starker Säuren und anschließender Reduktion der entstandenen 2-Hydroxy-3-phenyl-acrylsäuren erhalten werden.

Die Ausgangsverbindungen der allgemeinen Formel (VI) erhält man beispielsweise durch Umsetzung von Aminen der allgemeinen Formel HNR^2R^3 mit 2-(Alkoxy-carbonylmethyl)-3-aryl-propansäuren und anschließende hydrolytische Abspaltung der Alkylgruppe. Die erforderlichen 2-(Alkoxycarbonylmethyl)-3-aryl-propansäuren können in Analogie zu literaturbekannten Methoden (David A. Evans, Leester D. Wu, John J. M. Wiener, Jeffrey S. Johnson, David H. B. Ripin und Jason S. Tedrow, J. Org.Chem 64, 6411-6417 [1999]; Saul G. Cohen und Aleksander Milovanovic, J. Am. Chem. Soc. 90, 3495-3502 [1968]; Hiroyuki Kawano, Youichi Ishii, Takao Ikariya, Masahiko Saburi, Sadao Yoshikawa, Yasuzo Uchida und Hidenori Kumobayashi, Tetrahedron Letters 28, 1905-1908 [1987]) hergestellt werden. Carbonsäuren der allgemeinen Formel (VIII) können nach den in der WO 98/11128 angegebenen Verfahren aus allgemein zugänglichen Ausgangsmaterialien hergestellt werden.

Die erhaltenen Verbindungen der allgemeinen Formel (I) können, sofern sie geeignete basische Funktionen enthalten, insbesondere für pharmazeutische Anwendungen in ihre physiologisch verträglichen Salze mit anorganischen oder organischen Säuren übergeführt werden. Als Säuren kommen hierfür beispielsweise Salzsäure, Bromwasserstoffsäure, Phosphorsäure, Salpetersäure, Schwefelsäure, Methansulfonsäure, Ethansulfonsäure, Benzolsulfonsäure, *p*-Toluolsulfonsäure, Essigsäure, Fumarsäure, Bernsteinsäure, Milchsäure, Mandelsäure, Äpfelsäure, Zitronensäure, Weinsäure oder Maleinsäure in Betracht.

Die vorliegende Erfindung betrifft Racemate, sofern die Verbindungen der allgemeinen Formel (I) nur ein Chiralitätselement besitzen. Die Anmeldung umfasst jedoch auch die einzelnen diastereomeren Antipodenpaare oder deren Gemische,

die dann vorliegen, wenn mehr als ein Chiralitätselement in den Verbindungen der allgemeinen Formel (I) vorhanden ist, sowie die einzelnen optisch aktiven Enantiomeren, aus denen sich die erwähnten Racemate zusammensetzen.

Ebenfalls mit vom Gegenstand dieser Erfindung umfasst sind die erfindungsgemäßen Verbindungen, einschließlich deren Salze, in denen ein oder mehrere Wasserstoffatome durch Deuterium ausgetauscht sind.

Die neuen Verbindungen der allgemeinen Formel (I) und deren physiologisch verträgliche Salze weisen wertvolle pharmakologische Eigenschaften auf, die auf ihre selektiven CGRP-antagonistischen Eigenschaften zurückgehen. Ein weiterer Gegenstand der Erfindung sind diese Verbindungen enthaltende Arzneimittel, deren Verwendung und deren Herstellung.

Die voranstehend genannten neuen Verbindungen und deren physiologisch verträgliche Salze besitzen CGRP-antagonistische Eigenschaften und zeigen gute Affinitäten in CGRP-Rezeptorbindungsstudien. Die Verbindungen weisen in den nachstehend beschriebenen pharmakologischen Testsystemen CGRP-antagonistische Eigenschaften auf.

Zum Nachweis der Affinität der voranstehend genannten Verbindungen zu humanen CGRP-Rezeptoren und ihrer antagonistischen Eigenschaften wurden die folgenden Versuche durchgeführt:

A. Bindungsstudien mit (den humanen CGRP-Rezeptor exprimierenden) SK-N-MC-Zellen

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SK-N-MC-Zellen werden in "Dulbecco's modified Eagle Medium" kultiviert. Das Medium konfluenter Kulturen wird entfernt. Die Zellen werden zweimal mit PBS-Puffer (Gibco 041-04190 M) gewaschen, durch Zugabe von PBS-Puffer, versetzt mit 0.02% EDTA, abgelöst und durch Zentrifugation isoliert. Nach Resuspension in 20 ml "Balanced Salts Solution" [BSS (in mM): NaCl 120, KCl 5.4, $NaHCO_3$ 16.2, $MgSO_4$ 0.8, $NaHPO_4$ 1.0, $CaCl_2$ 1.8, D-Glucose 5.5, HEPES 30, pH 7.40] werden die Zellen

zweimal bei 100 x g zentrifugiert und in BSS resuspendiert. Nach Bestimmung der Zellzahl werden die Zellen mit Hilfe eines Ultra-Turrax homogenisiert und für 10 Minuten bei 3000 x g zentrifugiert. Der Überstand wird verworfen und das Pellet in Tris-Puffer (10 mM Tris, 50 mM NaCl, 5 mM $MgCl_2$, 1 mM EDTA, pH 7.40), angereichert mit 1% Rinderserum-Albumin und 0.1% Bacitracin, rezentrifugiert und resuspendiert (1 ml / 1000000 Zellen). Das Homogenat wird bei -80°C eingefroren. Die Membranpräparationen sind bei diesen Bedingungen für mehr als 6 Wochen stabil.

Nach Auftauen wird das Homogenat 1:10 mit Assay-Puffer (50 mM Tris, 150 mM NaCl, 5 mM $MgCl_2$, 1 mM EDTA, pH 7.40) verdünnt und 30 Sekunden lang mit einem Ultra-Turrax homogenisiert. 230 µl des Homogenats werden für 180 Minuten bei Raumtemperatur mit 50 pM ^{125}I-Iodotyrosyl-Calcitonin-Gene-Related Peptide (Amersham) und ansteigenden Konzentrationen der Testsubstanzen in einem Gesamtvolumen von 250 µl inkubiert. Die Inkubation wird durch rasche Filtration durch mit Polyethylenimin (0.1%) behandelte GF/B-Glasfaserfilter mittels eines Zellharvesters beendet. Die an Protein gebundene Radioaktivität wird mit Hilfe eines Gammacounters bestimmt. Als nichtspezifische Bindung wird die gebundene Radioaktivität nach Gegenwart von 1 µM humanem CGRP-alpha während der Inkubation definiert.

Die Analyse der Konzentrations-Bindungskurven erfolgt mit Hilfe einer computergestützten nichtlinearen Kurvenanpassung.

Die eingangs erwähnten Verbindungen zeigen in dem beschriebenen Test IC_{50}-Werte ≤ 10000 nM.

B. CGRP-Antagonismus in SK-N-MC-Zellen

SK-N-MC-Zellen (1 Mio. Zellen) werden zweimal mit 250 µl Inkubationspuffer (Hanks' HEPES, 1 mM 3-Isobutyl-1-methylxanthin, 1% BSA, pH 7.4) gewaschen und bei 37°C für 15 Minuten vorinkubiert. Nach Zugabe von CGRP (10 µl) als Agonist in steigenden Konzentrationen (10^{-11} bis 10^{-6} M) bzw. zusätzlich von Substanz in 3 bis

4 verschiedenen Konzentrationen wird nochmals 15 Minuten inkubiert.

Intrazelluläres cAMP wird anschließend durch Zugabe von 20 µl 1M HCl und Zentrifugation (2000 x g, 4°C für 15 Minuten) extrahiert. Die Überstände werden in flüssigem Stickstoff eingefroren und bei –20°C gelagert.

Die cAMP-Gehalte der Proben werden mittels Radioimmunassay (Fa. Amersham) bestimmt und die pA_2-Werte antagonistisch wirkender Substanzen graphisch ermittelt.

Die erfindungsgemäßen Verbindungen zeigen in dem beschriebenen *in vitro* Testmodell CGRP-antagonistische Eigenschaften in einem Dosisbereich zwischen 10^{-12} bis 10^{-5} M.

Aufgrund ihrer pharmakologischen Eigenschaften eignen sich die erfindungsgemäßen Verbindungen und deren Salze mit physiologisch verträglichen Säuren somit zur akuten und prophylaktischen Behandlung von Kopfschmerzen, insbesondere Migräne- bzw. Cluster-Kopfschmerz. Weiterhin beeinflussen die erfindungsgemäßen Verbindungen auch die folgenden Erkrankungen positiv: Nicht-insulinabhängigen Diabetes mellitus ("NIDDM"), complex regional pain syndrome (CRPS1), cardiovaskuläre Erkrankungen, Morphintoleranz, Clostritiumtoxin-bedingte Durchfallerkrankungen, Erkrankungen der Haut, insbesondere thermische und strahlenbedingte Hautschäden inklusive Sonnenbrand, entzündliche Erkrankungen, z.B. entzündliche Gelenkerkrankungen (Arthritis), neurogene Entzündungen der oralen Mucosa, entzündliche Lungenerkrankungen, allergische Rhinitis, Asthma, Erkrankungen, die mit einer überschießenden Gefäßerweiterung und dadurch bedingter verringerter Gewebedurchblutung einhergehen, z.B. Schock und Sepsis. Darüber hinaus zeigen die erfindungsgemäßen Verbindungen eine lindernde Wirkung auf Schmerzzustände im allgemeinen.
Die Symptomatik menopausaler, durch Gefäßerweiterung und erhöhten Blutfluß verursachter Hitzewallungen östrogendefizienter Frauen sowie hormonbehandelter Prostatakarzinompatienten wird durch die CGRP-Antagonisten der vorliegenden Anwendung präventiv und akut-therapeutisch günstig beeinflußt, wobei sich dieser

Therapieansatz vor der Hormonsubstitution durch Nebenwirkungsarmut auszeichnet.

Die zur Erzielung einer entsprechenden Wirkung erforderliche Dosierung beträgt zweckmäßigerweise bei intravenöser oder subkutaner Gabe 0.01 bis 3 mg/kg Körpergewicht, vorzugsweise 0.01 bis 1 mg/kg Körpergewicht, bei oraler Gabe 0.01 bis 20 mg/kg Körpergewicht, vorzugsweise 0.1 bis 10 mg/kg Körpergewicht, und bei nasaler oder inhalativer Gabe 0.01 bis 10 mg/kg Körpergewicht, vorzugsweise 0.1 bis 10 mg/kg Körpergewicht, jeweils 1 bis 3 x täglich.

Sofern die Behandlung mit CGRP-Antagonisten oder/und CGRP-Release-Hemmern in Ergänzung zu einer üblichen Hormonsubstitution erfolgt, empfiehlt sich eine Verringerung der vorstehend angegebenen Dosierungen, wobei die Dosierung dann 1/5 der vorstehend angegebenen Untergrenzen bis zu 1/1 der vorstehend angegebenen Obergrenzen betragen kann.

Die erfindungsgemäß hergestellten Verbindungen können entweder alleine oder gegebenenfalls in Kombination mit anderen Wirksubstanzen zur Behandlung von Migräne intravenös, subkutan, intramuskulär, intrarektal, intranasal, durch Inhalation, transdermal oder oral erfolgen, wobei zur Inhalation insbesondere Aerosol-formulierungen geeignet sind. Die Kombinationen können entweder simultan oder sequentiell verabreicht werden.

Als Kombinationspartner denkbare Wirkstoffklassen sind z.B. Angiotensin-II Rezeptorantagonisten, α-Agonisten und α-Antagonisten, 5-$HT_{1B/1D}$-Agonisten, AMPA-Antagonisten, schwachen Analgetica, Antidepressiva, Antiemetika, Antikonvulsiva, Antimuscarinika, β-Blocker, Calcium-Antagonisten, Corticosteroide, Ergot-Alkaloiden, Histamin-H1-Rezeptorantagonisten, Neurokinin-Antagonisten, Neuroleptika, nichtsteroidale Antiphlogistika, NO-Synthase-Hemmer, Prokinetika, selektive Serotonin-Wiederaufnahme-Hemmer oder andere Antimigränemitteln, die zusammen mit einem oder mehreren inerten üblichen Trägerstoffen und/oder Verdünnungsmitteln, z.B. mit Maisstärke, Milchzucker, Rohrzucker, mikrokristalliner Zellulose, Magnesiumstearat, Polyvinylpyrrolidon, Zitronensäure, Weinsäure, Wasser, Wasser/Ethanol, Wasser/Glycerin, Wasser/Sorbit, Wasser/Polyethylen-

glykol, Propylenglykol, Cetylstearylalkohol, Carboxymethylcellulose oder fetthaltigen Substanzen wie Hartfett oder deren geeigneten Gemischen, in übliche galenische Zubereitungen wie Tabletten, Dragées, Kapseln, Pulver, Suspensionen, Lösungen, Dosieraerosole oder Zäpfchen eingearbeitet werden können.

Für die oben erwähnten Kombinationen kommen somit als weitere Wirksubstanzen beispielsweise die nicht-steroidalen Antiphlogistika Aceclofenac, Acemetacin, Acetylsalicylsäure, Azathioprin, Diclofenac, Diflunisal, Fenbufen, Fenoprofen, Flurbiprofen, Ibuprofen, Indometacin, Ketoprofen, Leflunomid, Lornoxicam, Mefenaminsäure, Naproxen, Phenylbutazon, Piroxicam, Sulfasalazin, Tenoxicam, Zomepirac oder deren physiologisch verträgliche Salze sowie Meloxicam und andere selektive COX2-Inhibitoren, wie beispielsweise Rofecoxib und Celecoxib, in Betracht.

Weiterhin können z.B. Candesartan, Eprosartan, Irbesartan, Losartan, Olmesartan, Tasosartan, Telmisartan, Valsartan, Duloxetin, Ergotamin, Dihydroergotamin, Metoclopramid, Domperidon, Diphenhydramin, Cyclizin, Promethazin, Chlorpromazin, Vigabatrin, Timolol, Isomethepten, Pizotifen, Botox, Gabapentin, Topiramat, Riboflavin, Montelukast, Lisinopril, Prochlorperazin, Dexamethason, Flunarizin, Dextropropoxyphen, Meperidin, Metoprolol, Propranolol, Nadolol, Atenolol, Clonidin, Indoramin, Carbamazepin, Phenytoin, Valproat, Amitryptilin, Lidocain oder Diltiazem und andere 5-$HT_{1B/1D}$-Agonisten wie z.B. Almotriptan, Avitriptan, Donitriptan, Eletriptan, Frovatriptan, Naratriptan, Rizatriptan, Sumatriptan und Zolmitriptan sowie deren physiologisch verträgliche Salze verwendet werden.

Die Dosis für diese Wirksubstanzen beträgt hierbei zweckmäßigerweise 1/5 der üblicherweise empfohlenen niedrigsten Dosierung bis zu 1/1 der normalerweise empfohlenen Dosierung, also beispielsweise 20 bis 100 mg Sumatriptan.

Ein weiterer Gegenstand der Erfindung ist die Verwendung der erfindungsgemäßen Verbindungen als wertvolle Hilfsmittel zur Erzeugung und Reinigung (Affinitätschromatographie) von Antikörpern sowie, nach geeigneter radioaktiver Markierung, beispielsweise durch Tritiierung geeigneter Vorstufen, beispielsweise durch katalytische Hydrierung mit Trithium oder Ersatz von Halogenatomen durch Tritium,

in RIA- und ELISA-Assays und als diagnostische bzw. analytische Hilfsmittel in der Neurotransmitter-Forschung.

Experimenteller Teil

Für die hergestellten Verbindungen liegen in der Regel IR-, ^{1}H-NMR und/oder Massenspektren vor.

Wenn nicht anders angegeben, werden R_f-Werte unter Verwendung von DC-Fertigplatten Kieselgel 60 F254 (E. Merck, Darmstadt, Artikel-Nr. 1.05714) ohne Kammersättigung bestimmt. Die bei den Fliessmitteln angegebenen Verhältnisse beziehen sich auf Volumeneinheiten der jeweiligen Lösungsmittel. Die angegebenen Volumeneinheiten bei NH_3 beziehen sich auf eine konzentrierte Lösung von NH_3 in Wasser.

Soweit nicht anders vermerkt sind die bei den Aufarbeitungen der Reaktionslösungen verwendeten Säure-, Basen- und Salzlösungen wässrige Systeme der angegebenen Konzentrationen.

Zu chromatographischen Reinigungen wird Kieselgel der Firma Millipore (MATREX™, 35 bis 70 µm) verwendet.

Die angegebenen HPLC-Daten werden unter nachstehend angeführten Parametern gemessen:

Methode A:

Analytische Säule: Zorbax-Säule (Agilent Technologies), SB (Stable Bond) C18; 3.5 µm; 4.6 x 75 mm; Säulentemperatur: 30°C; Fluss: 0.8 mL / min; Injektionsvolumen: 5 µL; Detektion bei 254 nm

Zeit (min)	Volumenprozent Wasser (mit 0.1% Ameisensäure)	Volumenprozent Acetonitril (mit 0.1% Ameisensäure)
0	95	5
9	10	90
10	10	90
11	95	5

Bei präparativen HPLC-Reinigungen werden in der Regel die gleichen Gradienten verwendet, die bei der Erhebung der analytischen HPLC-Daten benutzt wurden. Die

Sammlung der Produkte erfolgt massengesteuert, die Produkt enthaltenden Fraktionen werden vereinigt und gefriergetrocknet.

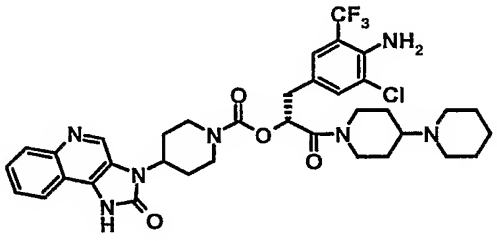
Falls nähere Angaben zur Konfiguration fehlen, bleibt offen, ob es sich um reine Enantiomere handelt oder ob partielle oder gar völlige Racemisierung eingetreten ist.

In den Versuchsbeschreibungen werden die folgenden Abkürzungen verwendet:

DCM	Dichlormethan
DMAP	4-Dimethylaminopyridin
DMF	*N*,*N*-Dimethylformamid
EtOAc	Essigsäureethylester
HCl	Salzsäure
LiOH	Lithiumhydroxid
MeOH	Methanol
RT	Raumtemperatur
TBTU	2-(1*H*-Benzotriazol-1-yl)-1,1,3,3-tetramethyluronium-Tetrafluorborat
THF	Tetrahydrofuran

Beispiel 1

4-(2-Oxo-1,2-dihydro-imidazo[4,5-*c*]chinolin-3-yl)-piperidin-1-carbonsäure-(*R*)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-[1,4']bipiperidinyl-1'-yl-2-oxo-ethylester



(1a) 4-(2-Oxo-1,2-dihydro-imidazo[4,5-*c*]chinolin-3-yl)-piperidin-1-carbonsäure-(*R*)-2-(4-amino-3-chlor-5-trifluormethyl-phenyl)-1-ethoxycarbonyl-ethylester

Zu der Mischung aus 0.79 g (6.42 mmol) DMAP und 100 mL Pyridin wurden 1.29 g (6.42 mmol) 4-Chlorameisensäure-4-nitrophenylester zugegeben und 1 h bei RT

gerührt. Danach wurde eine Lösung von 2.0 g (6.42 mmol) (R)-3-(4-Amino-3-chlor-5-trifluormethyl-phenyl)-2-hydroxy-propionsäureethylester in 15 mL Pyridin unter Rühren bei RT zugetropft und weitere 2 h bei RT gerührt. Anschließend wurde die Mischung mit 1.72 g (6.42 mmol) 3-Piperidin-4-yl-1,3-dihydro-imidazo[4,5-*c*]chinolin-2-on versetzt und 2 Tage bei RT gerührt. Das Reaktionsgemisch wurde unter vermindertem Druck eingeengt, mit 200 mL EtOAc und 200 mL 15% K_2CO_3-Lösung versetzt, die organische Phase abgetrennt, getrocknet und eingeengt. Der Rückstand wurde säulenchromatographisch (Kieselgel, Gradient DCM zu DCM/MeOH/NH_3 0:95:5) gereinigt.

Ausbeute: 1.2 g (31% der Theorie)
ESI-MS: $(M+H)^+$ = 606/608 (Cl)
Retentionszeit (HPLC): 6.7 min (Methode A)

(1b) 4-(2-Oxo-1,2-dihydro-imidazo[4,5-*c*]chinolin-3-yl)-piperidin-1-carbonsäure-(*R*)-2-(4-amino-3-chlor-5-trifluormethyl-phenyl)-1-carboxy-ethylester

1.20 g (1.98 mmol) 4-(2-Oxo-1,2-dihydro-imidazo[4,5-*c*]chinolin-3-yl)-piperidin-1-carbonsäure-(R)-2-(4-amino-3-chlor-5-trifluormethyl-phenyl)-1-ethoxycarbonyl-ethyl-ester, gelöst in 30 mL THF, wurde bei RT mit einer Lösung von 74 mg (3.0 mmol) LiOH in 30 mL Wasser versetzt und 3 h bei RT gerührt. Das Reaktionsgemisch wurde unter vermindertem Druck eingeengt, der Rückstand mit 100 mL Wasser versetzt und mit 1 M HCl angesäuert. Der Niederschlag wurde abgesaugt, mit 50 mL Wasser gewaschen und im Umlufttrockenschrank getrocknet.

Ausbeute: 0.88 g (77% der Theorie)
ESI-MS: $(M+H)^+$ = 578/580 (Cl)
Retentionszeit (HPLC): 5.8 min (Methode A)

(1c) 4-(2-Oxo-1,2-dihydro-imidazo[4,5-*c*]chinolin-3-yl)-piperidin-1-carbonsäure-(*R*)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-[1,4']bipiperidinyl-1'-yl-2-oxo-ethylester

Eine Mischung aus 80 mg (0.138 mmol) 4-(2-Oxo-1,2-dihydro-imidazo[4,5-*c*]chinolin-3-yl)-piperidin-1-carbonsäure-(R)-2-(4-amino-3-chlor-5-trifluormethyl-phenyl)-1-carboxy-ethylester, 23.6 mg (0.14 mmol) [1,4']Bipiperidinyl, 46.6 mg (0.14 mmol) TBTU, 0.041 mL (0.28 mmol) Triethylamin und 1.8 mL DMF wurde über Nacht bei RT

gerührt. Das Reaktionsgemisch wurde direkt mittels HPLC-MS (Säule: Agilent Zorbax Stable Bond RP C18, 5 µM, 30x100 mm; Fluss 30 mL/min; Gradient: Wasser/Acetonitril) und anschließender Lyophilisation aufgereinigt.

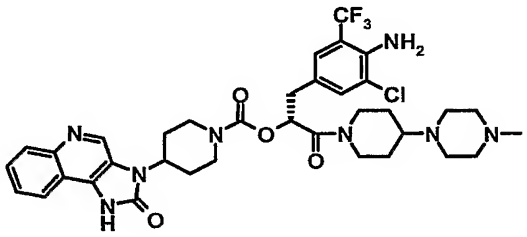
Ausbeute: 77 mg (76% der Theorie)

ESI-MS: $(M+H)^+$ = 728/730 (Cl)

Retentionszeit (HPLC): 4.8 min (Methode A)

Beispiel 2

4-(2-Oxo-1,2-dihydro-imidazo[4,5-*c*]chinolin-3-yl)-piperidin-1-carbonsäure-(*R*)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-2-oxo-ethylester



Analog Beispiel (1c) wurden aus 80 mg (0.14 mmol) 4-(2-Oxo-1,2-dihydro-imidazo-[4,5-*c*]chinolin-3-yl)-piperidin-1-carbonsäure-(R)-2-(4-amino-3-chlor-5-trifluor-methyl-phenyl)-1-carboxy-ethylester und 25 mg (0.14 mmol) 1-Methyl-4-piperidin-4-yl-piperazin das Produkt erhalten.

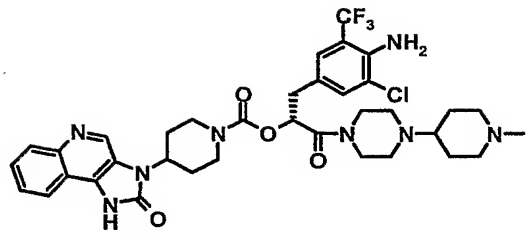
Ausbeute: 76 mg (74% der Theorie)

ESI-MS: $(M+H)^+$ = 743/745 (Cl)

Retentionszeit (HPLC): 5.5 min (Methode A)

Beispiel 3

4-(2-Oxo-1,2-dihydro-imidazo[4,5-*c*]chinolin-3-yl)-piperidin-1-carbonsäure-(*R*)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-[4-(1-methyl-piperidin-4-yl)-piperazin-1-yl]-2-oxo-ethylester



Analog Beispiel (1c) wurden aus 80 mg (0.14 mmol) 4-(2-Oxo-1,2-dihydro-imidazo-[4,5-*c*]chinolin-3-yl)-piperidin-1-carbonsäure-(*R*)-2-(4-amino-3-chlor-5-trifluormethyl-phenyl)-1-carboxy-ethylester und 26 mg (0.14 mmol) 1-(1-Methyl-piperidin-4-yl)-piperazin das Produkt erhalten.

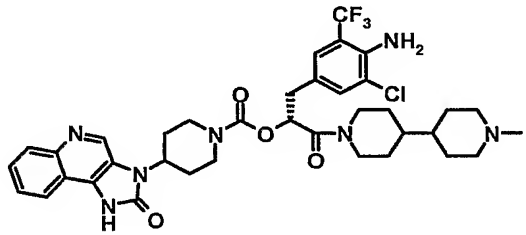
Ausbeute: 68 mg (66% der Theorie)

ESI-MS: $(M+H)^+$ = 743/745 (Cl)

Retentionszeit (HPLC): 4.0 min (Methode A)

Beispiel 4

4-(2-Oxo-1,2-dihydro-imidazo[4,5-*c*]chinolin-3-yl)-piperidin-1-carbonsäure-(*R*)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-(1'-methyl-[4,4']bipiperidinyl-1-yl)-2-oxo-ethyl ester



Analog Beispiel (1c) wurden aus 80 mg (0.14 mmol) 4-(2-Oxo-1,2-dihydro-imidazo-[4,5-*c*]chinolin-3-yl)-piperidin-1-carbonsäure-(*R*)-2-(4-amino-3-chlor-5-trifluor-methyl-phenyl)-1-carboxy-ethylester und 25 mg (0.14 mmol) 1-Methyl-[4,4']bipiperidinyl das Produkt erhalten.

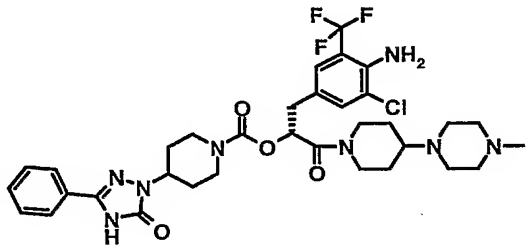
Ausbeute: 73 mg (71% der Theorie)

ESI-MS: $(M+H)^+$ = 742/744 (Cl)

Retentionszeit (HPLC): 4.9 min (Methode A)

Beispiel 5

4-(5-Oxo-3-phenyl-4,5-dihydro-[1,2,4]triazol-1-yl)-piperidin-1-carbonsäure-(*R*)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-2-oxo-ethylester



(5a) 4-(5-Oxo-3-phenyl-4,5-dihydro-[1,2,4]triazol-1-yl)-piperidin-1-carbonsäure-(*R*)-2-(4-amino-3-chlor-5-trifluormethyl-phenyl)-1-ethoxycarbonyl-ethylester

Analog Beispiel (1a) wurden aus 2.0 g (6.42 mmol) (*R*)-3-(4-Amino-3-chlor-5-trifluormethyl-phenyl)-2-hydroxy-propionsäureethylester und 2.41 g (65%, 6.42 mmol) 5-Phenyl-2-piperidin-4-yl-2,4-dihydro-1,2,4-triazol-3-on das Produkt erhalten werden.

Ausbeute:	1.0 g (27% der Theorie)
ESI-MS:	$(M+H)^+$ = 582/584 (Cl)
Retentionszeit (HPLC):	8.9 min (Methode A)

(5b) 4-(5-Oxo-3-phenyl-4,5-dihydro-[1,2,4]triazol-1-yl)-piperidin-1-carbonsäure-(*R*)-2-(4-amino-3-chlor-5-trifluormethyl-phenyl)-1-carboxy-ethylester

Analog Beispiel (1b) wurden aus 1.0 g (1.72 mmol) 4-(5-Oxo-3-phenyl-4,5-dihydro-[1,2,4]triazol-1-yl)-piperidin-1-carbonsäure-(*R*)-2-(4-amino-3-chlor-5-trifluormethyl-phenyl)-1-ethoxycarbonyl-ethylester und 64 mg (2.60 mmol) LiOH das Produkt erhalten werden.

Ausbeute:	0.91 g (96% der Theorie)
ESI-MS:	$(M+H)^+$ = 554/556 (Cl)
Retentionszeit (HPLC):	7.5 min (Methode A)

(5c) 4-(5-Oxo-3-phenyl-4,5-dihydro-[1,2,4]triazol-1-yl)-piperidin-1-carbonsäure-(*R*)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-2-oxo-ethylester

Analog Beispiel (1c) wurden aus 77 mg (0.14 mmol) 4-(5-Oxo-3-phenyl-4,5-dihydro-[1,2,4]triazol-1-yl)-piperidin-1-carbonsäure-(*R*)-2-(4-amino-3-chlor-5-trifluormethyl-phenyl)-1-carboxy-ethylester und 25 mg (0.14 mmol) 1-Methyl-4-piperidin-4-yl-piperazin das Produkt erhalten.

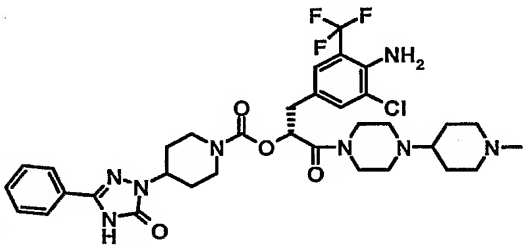
Ausbeute: 84 mg (84% der Theorie)

ESI-MS: $(M+H)^+$ = 719/721 (Cl)

Retentionszeit (HPLC): 5.4 min (Methode A)

Beispiel 6

4-(5-Oxo-3-phenyl-4,5-dihydro-[1,2,4]triazol-1-yl)-piperidin-1-carbonsäure (R)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-[4-(1-methyl-piperidin-4-yl)-piperazin-1-yl]-2-oxo-ethylester



Analog Beispiel (1c) wurden aus 77 mg (0.14 mmol) 4-(5-Oxo-3-phenyl-4,5-dihydro-[1,2,4]triazol-1-yl)-piperidin-1-carbonsäure-(*R*)-2-(4-amino-3-chlor-5-trifluormethyl-phenyl)-1-carboxy-ethylester und 26 mg (0.14 mmol) 1-(1-Methyl-piperidin-4-yl)-piperazin das Produkt erhalten.

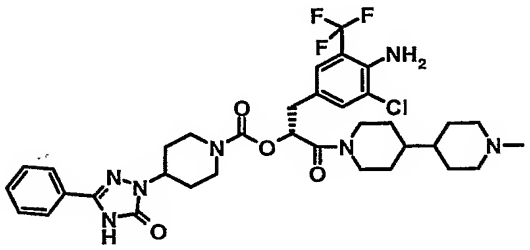
Ausbeute: 84 mg (84% der Theorie)

ESI-MS: $(M+H)^+$ = 719/721 (Cl)

Retentionszeit (HPLC): 5.0 min (Methode A)

Beispiel 7

4-(5-Oxo-3-phenyl-4,5-dihydro-[1,2,4]triazol-1-yl)-piperidin-1-carbonsäure-(R)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-(1'-methyl-[4,4']bipiperidinyl-1-yl)-2-oxo-ethyl ester

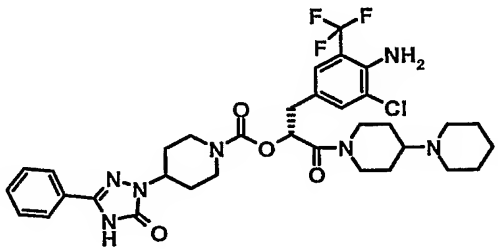


Analog Beispiel (1c) wurden aus 77 mg (0.14 mmol) 4-(5-Oxo-3-phenyl-4,5-dihydro-[1,2,4]triazol-1-yl)-piperidin-1-carbonsäure-(*R*)-2-(4-amino-3-chlor-5-trifluormethyl-phenyl)-1-carboxy-ethylester und 25 mg (0.14 mmol) 1-Methyl-[4,4']bipiperidinyl das Produkt erhalten.

Ausbeute:	76 mg (76% der Theorie)
ESI-MS:	$(M+H)^+$ = 718/720 (Cl)
Retentionszeit (HPLC):	6.0 min (Methode A)

Beispiel 8

4-(5-Oxo-3-phenyl-4,5-dihydro-[1,2,4]triazol-1-yl)-piperidin-1-carbonsäure-(*R*)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-[1,4']bipiperidinyl-1'-yl-2-oxo-ethylester

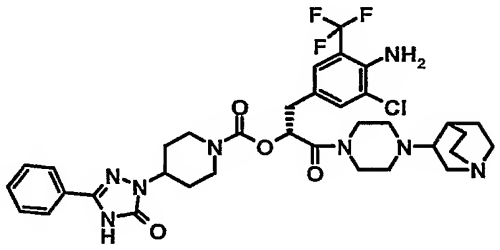


Analog Beispiel (1c) wurden aus 77 mg (0.14 mmol) 4-(5-Oxo-3-phenyl-4,5-dihydro-[1,2,4]triazol-1-yl)-piperidin-1-carbonsäure-(*R*)-2-(4-amino-3-chlor-5-trifluormethyl-phenyl)-1-carboxy-ethylester und 24 mg (0.14 mmol) [1,4']Bipiperidinyl das Produkt erhalten.

Ausbeute: 71 mg (73% der Theorie)
ESI-MS: $(M+H)^+$ = 704/706 (Cl)
Retentionszeit (HPLC): 6.0 min (Methode A)

Beispiel 9

4-(5-Oxo-3-phenyl-4,5-dihydro-[1,2,4]triazol-1-yl)-piperidin-1-carbonsäure-(*R*)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-[4-(1-aza-bicyclo[2.2.2]oct-3-yl)-piperazin-1-yl]-2-oxo-ethylester



Analog Beispiel (1c) wurden aus 77 mg (0.14 mmol) 4-(5-Oxo-3-phenyl-4,5-dihydro-[1,2,4]triazol-1-yl)-piperidin-1-carbonsäure-(*R*)-2-(4-amino-3-chlor-5-trifluormethyl-phenyl)-1-carboxy-ethylester und 27 mg (0.14 mmol) 3-Piperazin-1-yl-1-aza-bicyclo-[2.2.2]octan das Produkt erhalten.
Ausbeute: 13 mg (13% der Theorie)
ESI-MS: $(M+H)^+$ = 731/733(Cl)
Retentionszeit (HPLC): 5.6 min (Methode A)

Die nachfolgenden Beispiele beschreiben die Herstellung pharmazeutischer Anwendungsformen, die als Wirkstoff eine beliebige Verbindung der allgemeinen Formel (I) enthalten:

Beispiel I:

Kapseln zur Pulverinhalation mit 1 mg Wirkstoff

Zusammensetzung:

1 Kapsel zur Pulverinhalation enthält:

Wirkstoff	1.0 mg
Milchzucker	20.0 mg
Hartgelatinekapseln	50.0 mg
	71.0 mg

Herstellungsverfahren:

Der Wirkstoff wird auf die für Inhalativa erforderliche Korngröße gemahlen. Der gemahlene Wirkstoff wird mit dem Milchzucker homogen gemischt. Die Mischung wird in Hartgelatinekapseln abgefüllt.

Beispiel II:

Inhalationslösung für Respimat® mit 1 mg Wirkstoff

Zusammensetzung:

1 Hub enthält:

Wirkstoff	1.0	mg
Benzalkoniumchlorid	0.002	mg
Dinatriumedetat	0.0075	mg
Wasser gereinigt ad	15.0	µl

Herstellungsverfahren:

Der Wirkstoff und Benzalkoniumchlorid werden in Wasser gelöst und in Respimat®-Kartuschen abgefüllt.

Beispiel III:

Inhalationslösung für Vernebler mit 1 mg Wirkstoff

Zusammensetzung:

1 Fläschchen enthält:

Wirkstoff	0.1	g
Natriumchlorid	0.18	g
Benzalkoniumchlorid	0.002	g
Wasser gereinigt ad	20.0	ml

Herstellungsverfahren:
Wirkstoff, Natriumchlorid und Benzalkoniumchlorid werden in Wasser gelöst.

Beispiel IV:

Treibgas-Dosieraerosol mit 1 mg Wirkstoff

Zusammensetzung:
1 Hub enthält:

Wirkstoff	1.0	mg
Lecithin	0.1	%
Treibgas ad	50.0	µl

Herstellungsverfahren:
Der mikronisierte Wirkstoff wird in dem Gemisch aus Lecithin und Treibgas homogen suspendiert. Die Suspension wird in einen Druckbehälter mit Dosierventil abgefüllt.

Beispiel V:

Nasalspray mit 1 mg Wirkstoff

Zusammensetzung:

Wirkstoff	1.0	mg
Natriumchlorid	0.9	mg
Benzalkoniumchlorid	0.025	mg
Dinatriumedetat	0.05	mg
Wasser gereinigt ad	0.1	ml

Herstellungsverfahren:
Der Wirkstoff und die Hilfsstoffe werden in Wasser gelöst und in ein entsprechendes Behältnis abgefüllt.

Beispiel VI:

Injektionslösung mit 5 mg Wirksubstanz pro 5 ml

Zusammensetzung:

Wirksubstanz	5 mg
Glucose	250 mg
Human-Serum-Albumin	10 mg
Glykofurol	250 mg
Wasser für Injektionszwecke ad	5 ml

Herstellung:
Glykofurol und Glucose in Wasser für Injektionszwecke auflösen (Wfl); Human-Serum-Albumin zugeben; Wirkstoff unter Erwärmen auflösen; mit Wfl auf Ansatzvolumen auffüllen; unter Stickstoff-Begasung in Ampullen abfüllen.

Beispiel VII:

Injektionslösung mit 100 mg Wirksubstanz pro 20 ml

Zusammensetzung:

Wirksubstanz	100 mg
Monokaliumdihydrogen-phosphat = KH_2PO_4	12 mg
Dinatriumhydrogen phosphat = $Na_2HPO_4 \cdot 2H_2O$	2 mg
Natriumchlorid	180 mg
Human-Serum-Albumin	50 mg
Polysorbat 80	20 mg

Wasser für Injektionszwecke ad 20 ml

Herstellung:

Polysorbat 80, Natriumchlorid, Monokaliumdihydrogenphosphat und Dinatriumhydrogenphosphat in Wasser für Injektionszwecke (Wfl) auflösen; Human-Serum-Albumin zugeben; Wirkstoff unter Erwärmen auflösen; mit Wfl auf Ansatzvolumen auffüllen; in Ampullen abfüllen.

Beispiel VIII:

Lyophilisat mit 10 mg Wirksubstanz

Zusammensetzung:

Wirksubstanz	10 mg
Mannit	300 mg
Human-Serum-Albumin	20 mg

Herstellung:

Mannit in Wasser für Injektionszwecke (Wfl) auflösen; Human-Serum-Albumin zugeben; Wirkstoff unter Erwärmen auflösen; mit Wfl auf Ansatzvolumen auffüllen; in Vials abfüllen; gefriertrocknen.

Lösungsmittel für Lyophilisat:

Polysorbat 80 = Tween 80	20 mg
Mannit	200 mg
Wasser für Injektionszwecke ad	10 ml

Herstellung:

Polysorbat 80 und Mannit in Wasser für Injektionszwecke (Wfl) auflösen; in Ampullen abfüllen.

Beispiel IX:

Tabletten mit 20 mg Wirksubstanz

Zusammensetzung:

Wirksubstanz	20 mg
Lactose	120 mg
Maisstärke	40 mg
Magnesiumstearat	2 mg
Povidon K 25	18 mg

Herstellung:

Wirksubstanz, Lactose und Maisstärke homogen mischen; mit einer wässerigen Lösung von Povidon granulieren; mit Magnesiumstearat mischen; auf einer Tablettenpresse abpressen; Tablettengewicht 200 mg.

Beispiel X:

Kapseln mit 20 mg Wirksubstanz

Zusammensetzung:

Wirksubstanz	20 mg
Maisstärke	80 mg
Kieselsäure. hochdispers	5 mg
Magnesiumstearat	2.5 mg

Herstellung:

Wirksubstanz, Maisstärke und Kieselsäure homogen mischen; mit Magnesiumstearat mischen; Mischung auf einer Kapselfüllmaschine in Hartgelatine-Kapseln Grösse 3 abfüllen.

Beispiel XI:

Zäpfchen mit 50 mg Wirksubstanz

Zusammensetzung:

Wirksubstanz	50 mg
Hartfett (Adeps solidus) q.s. ad	1700 mg

Herstellung:

Hartfett bei ca. 38°C aufschmelzen; gemahlene Wirksubstanz im geschmolzenen Hartfett homogen dispergieren; nach Abkühlen auf ca. 35°C in vorgekühlte Formen ausgiessen.

Beispiel XII:

Injektionslösung mit 10 mg Wirksubstanz pro 1 ml

Zusammensetzung:

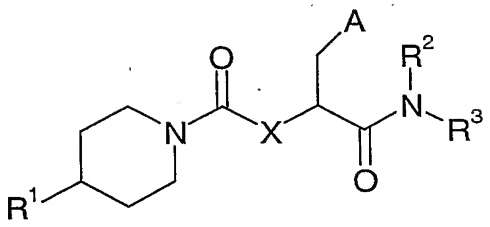
Wirksubstanz	10 mg
Mannitol	50 mg
Human-Serum-Albumin	10 mg
Wasser für Injektionszwecke ad	1 ml

Herstellung:

Mannitol in Wasser für Injektionszwecke auflösen (Wfl); Human-Serum-Albumin zugeben; Wirkstoff unter Erwärmen auflösen; mit Wfl auf Ansatzvolumen auffüllen; unter Stickstoff-Begasung in Ampullen abfüllen.

Patentansprüche

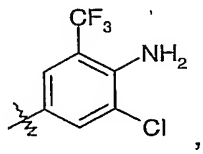
1. CGRP-Antagonisten der allgemeinen Formel



, (I)

in der

A einen Rest der Formel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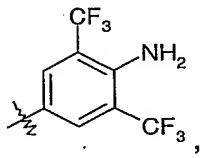
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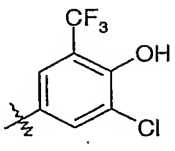
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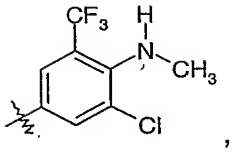
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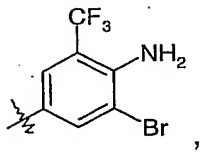
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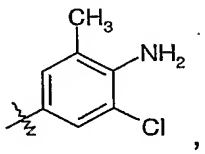
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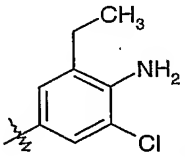
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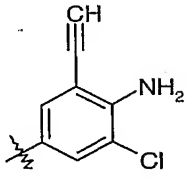
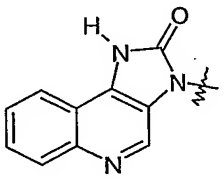

,

X ein Sauerstoffatom, eine Methylen- oder NH-Gruppe,

R^1 einen Rest der Formel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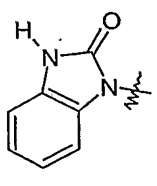
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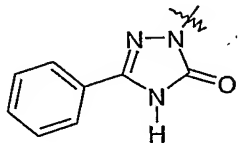
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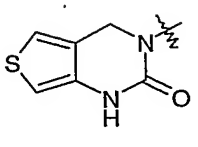
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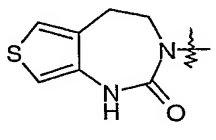
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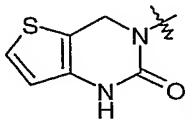
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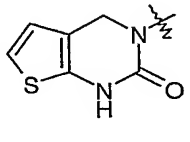
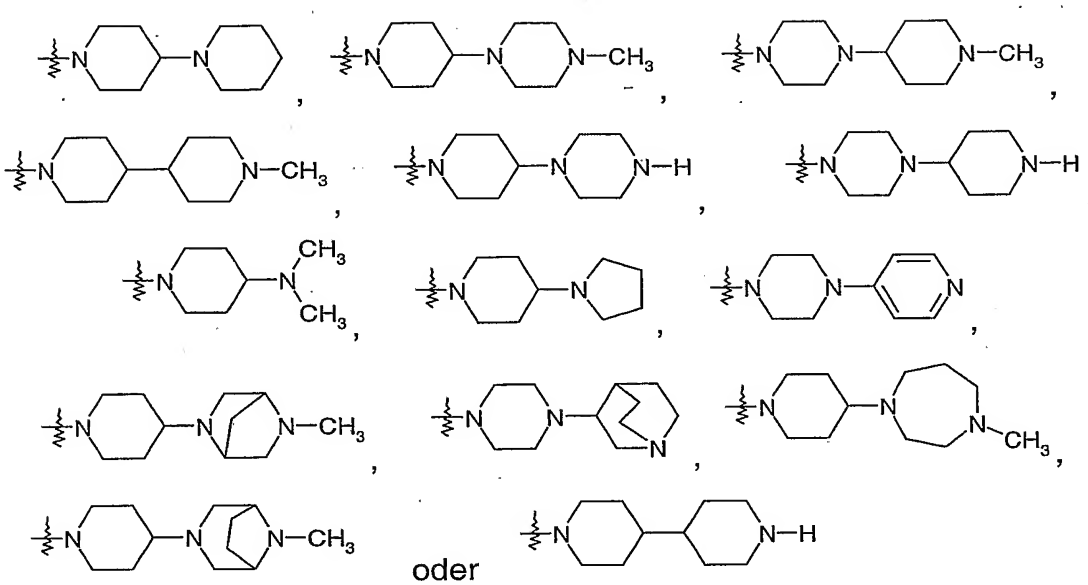

und

$-NR^2R^3$ einen Rest der Formel



oder

bedeutet,

deren Tautomere, deren Diastereomere, deren Enantiomere, deren Hydrate, deren Gemische und deren Salze sowie die Hydrate der Salze.

2. Die Verbindungen der allgemeinen Formel (I) gemäß Anspruch 1, die in der Tabelle der Beschreibung mit (1) bis (2353) fortlaufend nummeriert sind,

deren Tautomere, deren Diastereomere, deren Enantiomere, deren Hydrate, deren Gemische und deren Salze sowie die Hydrate der Salze.

3. Folgende Verbindungen der allgemeinen Formel (I) gemäß Anspruch 1:

(1) 4-(2-Oxo-1,2-dihydro-imidazo[4,5-*c*]chinolin-3-yl)-piperidin-1-carbonsäure-(*R*)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-[1,4']bipiperidinyl-1'-yl-2-oxo-ethylester,

(2) 4-(2-Oxo-1,2-dihydro-imidazo[4,5-*c*]chinolin-3-yl)-piperidin-1-carbonsäure-(*R*)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-2-oxo-ethylester,

(3) 4-(2-Oxo-1,2-dihydro-imidazo[4,5-*c*]chinolin-3-yl)-piperidin-1-carbonsäure-(*R*)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-[4-(1-methyl-piperidin-4-yl)-piperazin-1-yl]-2-oxo-ethylester,

(4) 4-(2-Oxo-1,2-dihydro-imidazo[4,5-*c*]chinolin-3-yl)-piperidin-1-carbonsäure-(*R*)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-(1'-methyl-[4,4']bipiperidinyl-1-yl)-2-oxo-ethylester,

(5) 4-(5-Oxo-3-phenyl-4,5-dihydro-[1,2,4]triazol-1-yl)-piperidin-1-carbonsäure-(*R*)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-2-oxo-ethylester,

(6) 4-(5-Oxo-3-phenyl-4,5-dihydro-[1,2,4]triazol-1-yl)-piperidin-1-carbonsäure (R)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-[4-(1-methyl-piperidin-4-yl)-piperazin-1-yl]-2-oxo-ethylester,

(7) 4-(5-Oxo-3-phenyl-4,5-dihydro-[1,2,4]triazol-1-yl)-piperidin-1-carbonsäure-(R)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-(1'-methyl-[4,4']bipiperidinyl-1-yl)-2-oxo-ethylester,

(8) 4-(5-Oxo-3-phenyl-4,5-dihydro-[1,2,4]triazol-1-yl)-piperidin-1-carbonsäure-(*R*)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-[1,4']bipiperidinyl-1'-yl-2-oxo-ethylester,

(9) 4-(5-Oxo-3-phenyl-4,5-dihydro-[1,2,4]triazol-1-yl)-piperidin-1-carbonsäure-(*R*)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-[4-(1-aza-bicyclo[2.2.2]oct-3-yl)-piperazin-1-yl]-2-oxo-ethylester,

deren Tautomere, deren Diastereomere, deren Enantiomere, deren Hydrate, deren Gemische und deren Salze sowie die Hydrate der Salze.

4. Physiologisch verträgliche Salze der Verbindungen gemäß einem der Ansprüche 1 bis 3 mit anorganischen oder organischen Säuren.

5. Arzneimittel, enthaltend eine Verbindung gemäß einem der Ansprüche 1 bis 3 oder ein physiologisch verträgliches Salz gemäß Anspruch 4 neben gegebenenfalls einem oder mehreren inerten Trägerstoffen und/oder Verdünnungsmitteln.

6. Verwendung einer Verbindung nach mindestens einem der Ansprüche 1 bis 4 zur Herstellung eines Arzneimittels zur akuten und prophylaktischen Behandlung von Kopfschmerzen, insbesondere Migräne- bzw. Cluster-Kopfschmerz.

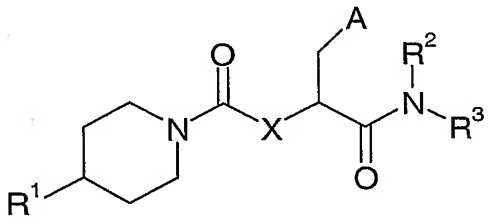
7. Verwendung einer Verbindung nach mindestens einem der Ansprüche 1 bis 4 zur Herstellung eines Arzneimittels zur Bekämpfung von nicht-insulinabhängigem Diabetes-mellitus (NIDDM).

8. Verwendung einer Verbindung nach mindestens einem der Ansprüche 1 bis 4 zur Herstellung eines Arzneimittels zur Behandlung von CRPS1 (complex regional pain syndrome), von cardiovaskulären Erkrankungen, von Morphintoleranz, von Chlostritiumtoxin-bedingten Durchfallerkrankungen, von Erkrankungen der Haut, insbesondere von thermischen und strahlungsbedingten Schäden inklusive Sonnenbrand, von entzündlichen Erkrankungen wie insbesondere entzündlicher Gelenkerkrankungen wie Arthritis, von neurogenen Entzündungen der oralen Mucosa, von entzündlichen Lungenerkrankungen, von allergischer Rhinitis, von Asthma, von Erkrankungen, die mit einer überschießenden Gefäßerweiterung und dadurch bedingter verringerter Gefäßdurchblutung, wie insbesondere Schock oder Sepsis, einhergeht, zur Linderung von Schmerzzuständen im allgemeinen oder zu präventiven oder akut therapeutischen Beeinflussung der durch Gefäßerweiterung und erhöhten Blutfluss verursachten Symptomatik von Hitzewallungen menopausaler, östrogendefizienter Frauen sowie hormonbehandelter Prostatakarzinompatienten.

9. Verfahren zur Herstellung eines Arzneimittels gemäß Anspruch 5, dadurch gekennzeichnet, dass auf nichtchemischem Weg eine Verbindung nach mindestens einem der Ansprüche 1 bis 4 in einen oder mehrere inerte Trägerstoffe und/oder Verdünnungsmittel eingearbeitet wird.

10. Verfahren zur Herstellung der Verbindungen der allgemeinen Formel (I) nach mindestens einem der Ansprüche 1 bis 4, dadurch gekennzeichnet, dass

(a) zur Herstellung von Verbindungen der allgemeinen Formel



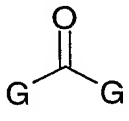
, (I)

in der X das Sauerstoffatom oder die NH-Gruppe bedeutet und A und R^1 bis R^3 wie in Anspruch 1 definiert sind, ein Piperidin der allgemeinen Formel

, (III)

in der R^1 in Anspruch 1 definiert ist,

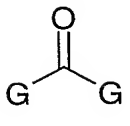
(i) mit einem Kohlensäurederivat der allgemeinen Formel



, (IV)

in der G eine nucleofuge Gruppe, die gleich oder verschieden sein kann, bedeutet, mit der Maßgabe, dass X die NH-Gruppe darstellt, oder

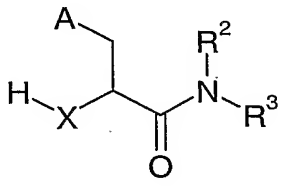
(ii) mit einem Kohlensäurederivat der allgemeinen Formel



, (IV)

in der G eine nucleofuge Gruppe, die gleich oder verschieden sein kann, bedeutet, mit der Maßgabe, dass X das Sauerstoffatom bedeutet,

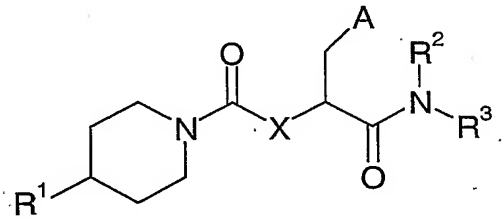
und mit einer Verbindung der allgemeinen Formel



, (V)

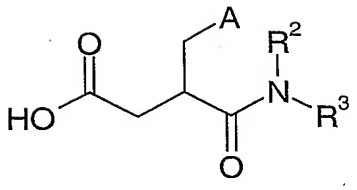
in der X das Sauerstoffatom oder eine –NH-Gruppe bedeutet und A, R^2 und R^3 wie in Anspruch 1 definiert sind, mit der Maßgabe, dass R^2 und R^3 keine weitere freie primäre oder sekundäre aliphatische Aminofunktion enthalten, umgesetzt wird; oder

(b) zur Herstellung von Verbindungen der allgemeinen Formel



, (I)

in der X die Methylengruppe bedeutet und A und R^1 bis R^3 wie in Anspruch 1 definiert sind, mit der Maßgabe, dass keine weitere freie primäre oder sekundäre aliphatische Aminofunktion enthalten, eine Carbonsäure der allgemeinen Formel



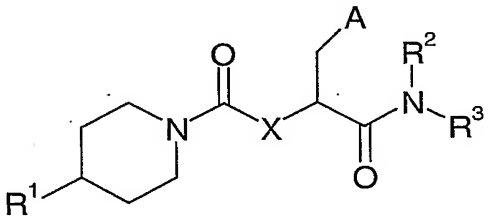
, (VI)

in der A, R^2 und R^3 wie in Anspruch 1 definiert sind, mit einem Piperidin der allgemeinen Formel

, (III)

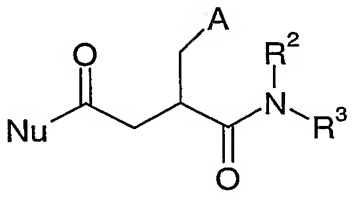
in der R^1 wie in Anspruch 1 definiert ist, gekuppelt wird; oder

(c) zur Herstellung von Verbindungen der allgemeinen Formel



, (I)

in der X die Methylengruppe bedeutet und A, R^2 und R^3 wie in Anspruch 1 definiert sind, mit der Maßgabe, dass diese Gruppen kein freies primäres oder sekundäres Amin enthalten, eine Verbindung der allgemeinen Formel



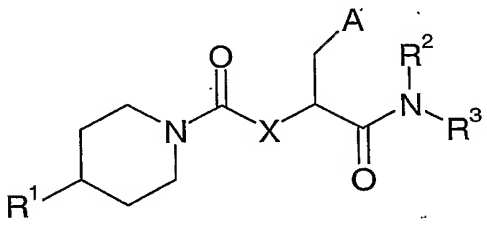
, (VII)

in der A, R^2 und R^3 wie in Anspruch 1 definiert sind, mit der Maßgabe, dass R^2 und R^3 kein freies primäres oder sekundäres Amin enthalten, und Nu eine Austrittsgruppe bedeutet, mit einem Piperidin der allgemeinen Formel

, (III)

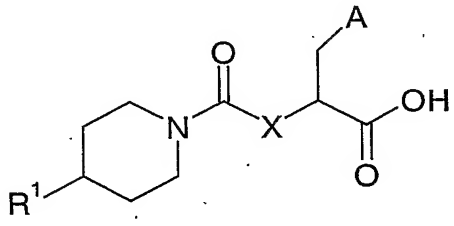
in der R^1 in Anspruch 1 definiert ist, gekuppelt wird; oder

(d) zur Herstellung von Verbindungen der allgemeinen Formel



, (I)

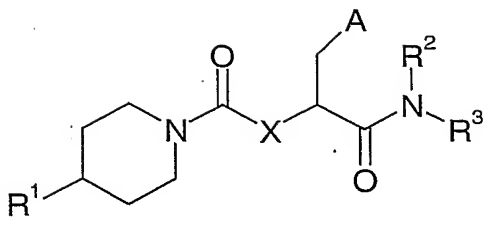
in der A, X und R^1 bis R^3 wie in Anspruch 1 definiert sind, eine Carbonsäure der allgemeinen Formel



, (VIII)

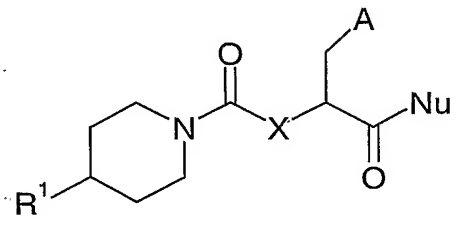
in der A, X und R^1 wie in Anspruch 1 definiert sind, mit einem Amin der allgemeinen Formel HNR^2R^3, in der R^2 und R^3 wie in Anspruch 1 definiert sind, mit der Maßgabe, dass sie keine weitere freie primäre oder sekundäre aliphatische Aminofunktion enthalten, gekuppelt wird; oder

(e) zur Herstellung von Verbindungen der allgemeinen Formel



, (I)

in der A, X und R^1 bis R^3 wie in Anspruch 1 definiert sind, mit der Maßgabe, dass kein freies primäres oder sekundäres Amin enthalten ist, eine Verbindung der allgemeinen Formel



, (IX)

in der A, X und R^1 wie in Anspruch 1 definiert sind und Nu eine Austrittsgruppe bedeutet, mit einem Amin der allgemeinen Formel HNR^2R^3, in der R^2 und R^3 wie in Anspruch 1 definiert sind, mit der Maßgabe, dass keine freie Carbonsäure- und/oder keine weitere freie primäre oder sekundäre aliphatische Aminofunktion enthalten ist, gekuppelt wird, und

erforderlichenfalls ein bei den vorstehend beschriebenen Umsetzungen verwendeter Schutzrest wieder abgespalten wird und/oder

gegebenenfalls verwendete Präcurserfunktionen in einer so erhaltenen Verbindung abgewandelt werden und/oder

gewünschtenfalls eine so erhaltene Verbindung der allgemeinen Formel (I) in ihre Stereoisomere aufgetrennt wird und/oder

eine so erhaltene Verbindung der allgemeinen Formel (I) in ihre Salze, insbesondere für die pharmazeutische Anwendung in ihre physiologisch verträglichen Salze übergeführt wird.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/003759

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D471/04 C07D235/26 C07D249/12 C07D495/04 C07D401/14
C07D487/08 C07D471/08 C07D451/04 C07D519/00 A61K31/437
A61K31/4184 A61K31/4196 A61K31/519 A61K31/551 A61P25/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, INSPEC, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MALLEE J J ET AL: "Receptor Activity-modifying Protein 1 Determines the Species Selectivity of Non-peptide CGRP Receptor Antagonists" JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, US, vol. 277, no. 16, 19 April 2002 (2002-04-19), pages 14294-14298, XP002271313 ISSN: 0021-9258 the whole document	1-10
Y	US 6 344 449 B1 (RUDOLF KLAUS ET AL) 5 February 2002 (2002-02-05) the whole document	1-10

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 August 2005	19/08/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Papathoma, S

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/003759

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 03/076432 A (BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG; HURNAUS, RUDOLF; RUDOLF, KL) 18 September 2003 (2003-09-18) abstract; claims 1-17; examples 53-76	1-10
Y	DE 102 27 294 A1 (BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG) 8 January 2004 (2004-01-08) the whole document	1-10
P,X	DE 102 50 080 A1 (BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG) 13 May 2004 (2004-05-13) abstract; claims 1-16; examples 17,19,21,22,24-27	1-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2005/003759

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6344449 B1	05-02-2002	DE 19636623 A1	12-03-1998
		DE 19720011 A1	19-11-1998
		AT 266673 T	15-05-2004
		AU 721035 B2	22-06-2000
		AU 4119697 A	02-04-1998
		BG 64214 B1	31-05-2004
		BG 103250 A	31-05-2000
		BR 9712023 A	31-08-1999
		CA 2262818 A1	19-03-1998
		CN 1230196 A ,C	29-09-1999
		CZ 9900823 A3	16-06-1999
		DE 59711622 D1	17-06-2004
		DK 927192 T3	13-09-2004
		EA 4037 B1	25-12-2003
		EE 9900115 A	15-10-1999
		WO 9811128 A1	19-03-1998
		EP 1440976 A1	28-07-2004
		EP 0927192 A1	07-07-1999
		ES 2221691 T3	01-01-2005
		HK 1021192 A1	30-04-2004
		HR 970481 A1	31-08-1998
		ID 21045 A	08-04-1999
		JP 3483893 B2	06-01-2004
		JP 2000505100 T	25-04-2000
		JP 2003300959 A	21-10-2003
		NO 991130 A	05-05-1999
		NZ 334543 A	23-06-2000
		PL 331989 A1	16-08-1999
		PT 927192 T	30-09-2004
		SI 927192 T1	31-10-2004
		SK 29799 A3	13-03-2000
		TR 9900537 T2	21-07-1999
		TW 477792 B	01-03-2002
		TW 498076 B	11-08-2002
		US 2001036946 A1	01-11-2001
		ZA 9708083 A	17-12-1999
		HU 9904501 A2	28-04-2000
		KR 2000044040 A	15-07-2000
		UA 68338 C2	15-08-2000
		US 2004214819 A1	28-10-2004
WO 03076432 A	18-09-2003	DE 10211770 A1	02-10-2003
		AU 2003212323 A1	22-09-2003
		CA 2476031 A1	18-09-2003
		WO 03076432 A1	18-09-2003
		EP 1487821 A1	22-12-2004
		US 2003236282 A1	25-12-2003
DE 10227294 A1	08-01-2004	AU 2003246414 A1	06-01-2004
		CA 2487716 A1	31-12-2003
		WO 2004000289 A2	31-12-2003
		EP 1517674 A2	30-03-2005
		US 2004076587 A1	22-04-2004
DE 10250080 A1	13-05-2004	AU 2003276156 A1	13-05-2004
		CA 2503455 A1	06-05-2004
		WO 2004037810 A1	06-05-2004
		EP 1558600 A1	03-08-2005

INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen
PCT/EP2005/003759

A. KLASSIFIZIERUNG DES ANMELDUNGSGEGENSTANDES

IPK 7 C07D471/04 C07D235/26 C07D249/12 C07D495/04 C07D401/14
C07D487/08 C07D471/08 C07D451/04 C07D519/00 A61K31/437
A61K31/4184 A61K31/4196 A61K31/519 A61K31/551 A61P25/06

Nach der Internationalen Patentklassifikation (IPK) oder nach der nationalen Klassifikation und der IPK

B. RECHERCHIERTE GEBIETE

Recherchierter Mindestprüfstoff (Klassifikationssystem und Klassifikationssymbole)
IPK 7 C07D A61K A61P

Recherchierte aber nicht zum Mindestprüfstoff gehörende Veröffentlichungen, soweit diese unter die recherchierten Gebiete fallen

Während der internationalen Recherche konsultierte elektronische Datenbank (Name der Datenbank und evtl. verwendete Suchbegriffe)
EPO-Internal, WPI Data, PAJ, BIOSIS, INSPEC, CHEM ABS Data

C. ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie°	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
A	MALLEE J J ET AL: "Receptor Activity-modifying Protein 1 Determines the Species Selectivity of Non-peptide CGRP Receptor Antagonists" JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, US, Bd. 277, Nr. 16, 19. April 2002 (2002-04-19), Seiten 14294-14298, XP002271313 ISSN: 0021-9258 das ganze Dokument	1-10
Y	US 6 344 449 B1 (RUDOLF KLAUS ET AL) 5. Februar 2002 (2002-02-05) das ganze Dokument	1-10

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[X] Weitere Veröffentlichungen sind der Fortsetzung von Feld C zu entnehmen

[X] Siehe Anhang Patentfamilie

° Besondere Kategorien von angegebenen Veröffentlichungen :
"A" Veröffentlichung, die den allgemeinen Stand der Technik definiert, aber nicht als besonders bedeutsam anzusehen ist
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"T" Spätere Veröffentlichung, die nach dem internationalen Anmeldedatum oder dem Prioritätsdatum veröffentlicht worden ist und mit der Anmeldung nicht kollidiert, sondern nur zum Verständnis des der Erfindung zugrundeliegenden Prinzips oder der ihr zugrundeliegenden Theorie angegeben ist
"X" Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann allein aufgrund dieser Veröffentlichung nicht als neu oder auf erfinderischer Tätigkeit beruhend betrachtet werden
"Y" Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann nicht als auf erfinderischer Tätigkeit beruhend betrachtet werden, wenn die Veröffentlichung mit einer oder mehreren anderen Veröffentlichungen dieser Kategorie in Verbindung gebracht wird und diese Verbindung für einen Fachmann naheliegend ist
"&" Veröffentlichung, die Mitglied derselben Patentfamilie ist

Datum des Abschlusses der internationalen Recherche	Absendedatum des internationalen Recherchenberichts
10. August 2005	19/08/2005

Name und Postanschrift der Internationalen Recherchenbehörde	Bevollmächtigter Bediensteter
Europäisches Patentamt, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Papathoma, S

C.(Fortsetzung) ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie°	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
Y	WO 03/076432 A (BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG; HURNAUS, RUDOLF; RUDOLF, KL) 18. September 2003 (2003-09-18) Zusammenfassung; Ansprüche 1-17; Beispiele 53-76	1-10
Y	DE 102 27 294 A1 (BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG) 8. Januar 2004 (2004-01-08) das ganze Dokument	1-10
P,X	DE 102 50 080 A1 (BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG) 13. Mai 2004 (2004-05-13) Zusammenfassung; Ansprüche 1-16; Beispiele 17,19,21,22,24-27	1-10

INTERNATIONALER RECHERCHENBERICHT

Angaben zu Veröffentlichungen, die zur selben Patentfamilie gehören

Internationales Aktenzeichen
PCT/EP2005/003759

Im Recherchenbericht angeführtes Patentdokument		Datum der Veröffentlichung	Mitglied(er) der Patentfamilie		Datum der Veröffentlichung
US 6344449	B1	05-02-2002	DE	19636623 A1	12-03-1998
			DE	19720011 A1	19-11-1998
			AT	266673 T	15-05-2004
			AU	721035 B2	22-06-2000
			AU	4119697 A	02-04-1998
			BG	64214 B1	31-05-2004
			BG	103250 A	31-05-2000
			BR	9712023 A	31-08-1999
			CA	2262818 A1	19-03-1998
			CN	1230196 A ,C	29-09-1999
			CZ	9900823 A3	16-06-1999
			DE	59711622 D1	17-06-2004
			DK	927192 T3	13-09-2004
			EA	4037 B1	25-12-2003
			EE	9900115 A	15-10-1999
			WO	9811128 A1	19-03-1998
			EP	1440976 A1	28-07-2004
			EP	0927192 A1	07-07-1999
			ES	2221691 T3	01-01-2005
			HK	1021192 A1	30-04-2004
			HR	970481 A1	31-08-1998
			ID	21045 A	08-04-1999
			JP	3483893 B2	06-01-2004
			JP	2000505100 T	25-04-2000
			JP	2003300959 A	21-10-2003
			NO	991130 A	05-05-1999
			NZ	334543 A	23-06-2000
			PL	331989 A1	16-08-1999
			PT	927192 T	30-09-2004
			SI	927192 T1	31-10-2004
			SK	29799 A3	13-03-2000
			TR	9900537 T2	21-07-1999
			TW	477792 B	01-03-2002
			TW	498076 B	11-08-2002
			US	2001036946 A1	01-11-2001
			ZA	9708083 A	17-12-1999
			HU	9904501 A2	28-04-2000
			KR	2000044040 A	15-07-2000
			UA	68338 C2	15-08-2000
			US	2004214819 A1	28-10-2004
WO 03076432	A	18-09-2003	DE	10211770 A1	02-10-2003
			AU	2003212323 A1	22-09-2003
			CA	2476031 A1	18-09-2003
			WO	03076432 A1	18-09-2003
			EP	1487821 A1	22-12-2004
			US	2003236282 A1	25-12-2003
DE 10227294	A1	08-01-2004	AU	2003246414 A1	06-01-2004
			CA	2487716 A1	31-12-2003
			WO	2004000289 A2	31-12-2003
			EP	1517674 A2	30-03-2005
			US	2004076587 A1	22-04-2004
DE 10250080	A1	13-05-2004	AU	2003276156 A1	13-05-2004
			CA	2503455 A1	06-05-2004
			WO	2004037810 A1	06-05-2004
			EP	1558600 A1	03-08-2005